Expedient Access to C-Aryl Linked Saturated Heterocyclic Motifs

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Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

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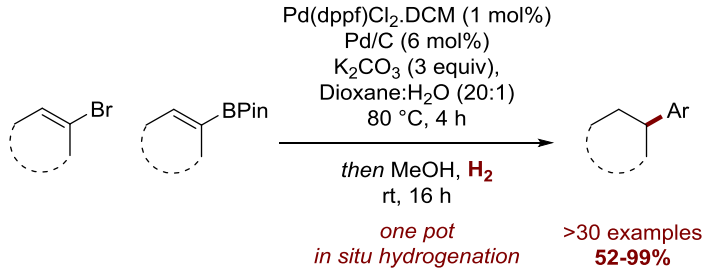
Abstract

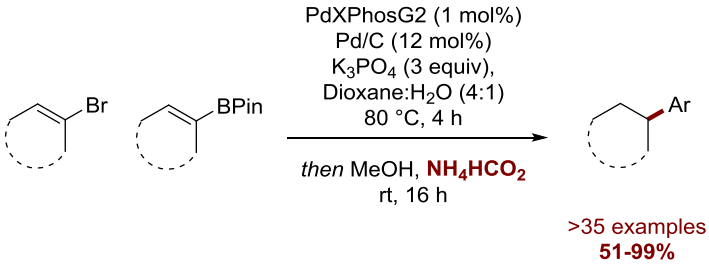
Over the past decade, there has been a significant increase in the overall degree of saturation in candidate molecules. Increased sp^3 character has been linked to a variety of improved physicochemical properties, including greater solubility and an improved likelihood of clinical success. Based on this, a range of methods have been developed to synthesise compounds with high saturation, particularly with respect to sp^2-sp^3 cross-coupling reactions. Many of these approaches suffer from severe drawbacks, such as a lack of generality and the requirement for bespoke, complex catalyst systems.

After initial investigation into a Suzuki-Miyaura approach towards the molecules of interest, the development of a one-pot Suzuki-Miyaura-hydrogenation was explored. This method was found to be highly general and tolerant of a wide range of functionalities.



Scheme 1: Developed Suzuki-Miyaura-hydrogenation methodology

Subsequently, the methodology was extended to allow for a transfer hydrogenation protocol. This process was broadly applicable to a range of synthetic methods, including an array format and the synthesis of multiple biologically active compounds.



Scheme 2: Developed Suzuki-Miyaura-transfer-hydrogenation methodology

Acknowledgements

Firstly, I would like to thank Dr Craig Jamieson for his guidance and encouragement over the past three and a half years. I have learned a huge amount under his supervision and I appreciate all the effort he has put in to developing me as a scientist.

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I owe an immeasurable amount of thanks to my family, who have been incredibly supportive throughout all aspects of my studies. Particularly to my parents, for always being there to listen, help and advise.

Finally, thank you to Julie for being a constant source of reassurance over the past seven years. I am indebted to her for her patience and company during my times of stress.

Abbreviations

9-BBN	9-Borabicyclo[3,3,1]nonane
AMPA	2-Amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid
APhos	(4-(*N*,*N*-Dimethylamino)phenyl)di-tert-butyl phosphine
ATH	Asymmetric transfer hydrogenation
BACE	Beta-secretase
BF_3K	Potassium trifluoroborate
BH_3	Borane
BINAP	(±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BPin	Pinacol borane
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Dan	1,8-diaminonapthalenyl
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DCM	Dichloromethane
DMB	2,4-Dimethoxybenzyl
DMF	Dimethylformamide
DMS	Dimethyl sulfide
dppb	diphenylphosphinobutane
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
ee	Enantiomeric excess
es	Enantiospecificity
Et_3N	Triethylamine
Et_2O	Diethyl ether

EtOAc	Ethyl Acetate
Fsp^3	Fraction sp^3
G2	2^{nd} generation
$(Ipc)_2BH$	Diisopinocampheylborane
$IpcBH_2$	Monoisopinocampheylborane
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
MeCN	Acetonitrile
MIDA	*N*-methyliminodiacetic acid
NHC	*N*-heterocyclic carbene
nr	No reaction
PdXPhosG2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
PCA	Principal Component Analysis
PE	Petroleum Ether
RBF	Round bottom flask
RO5	Rule of five
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SM	Suzuki-Miyaura
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBDMS	*tert*-Butyldimethylsilyl
TH	Transfer hydrogenation
THF	Tetrahydrofuran
TM	Transition metal
TMEDA	Tetramethylethylenediamine
UV	Ultraviolet

XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Contents

1. Introduction

1.1 Saturation in Drug Compounds

Since the publication of Lipinski's seminal 'Rule of Five" (RO5),[1] the pharmaceutical industry has become increasingly more concerned with the physicochemical properties of drug and candidate molecules. A multitude of metrics have since been introduced in order to estimate a compound's likelihood of achieving chemical success, and these are routinely calculated and considered throughout each stage of the drug discovery process. In addition to this, the last decade has seen an increased consideration of the complexity of compounds synthesised within a pharmaceutical setting. Lovering's 2009 paper entitled *Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success* suggests that a key descriptor for a compound's complexity is the fraction sp^3 (Fsp^3 = number of sp^3 hybridized carbons/total carbon count).[2] This analysis indicates that greater saturation bestows three dimensionality, which allows compounds to access a broader degree of chemical space, as well as improving physicochemical properties such as solubility and melting point. Most importantly, a higher Fsp^3 has been linked to an increased chance of clinical success. As Figure 1 indicates, the average Fsp^3 increases steadily when progressing through the stages of drug development.

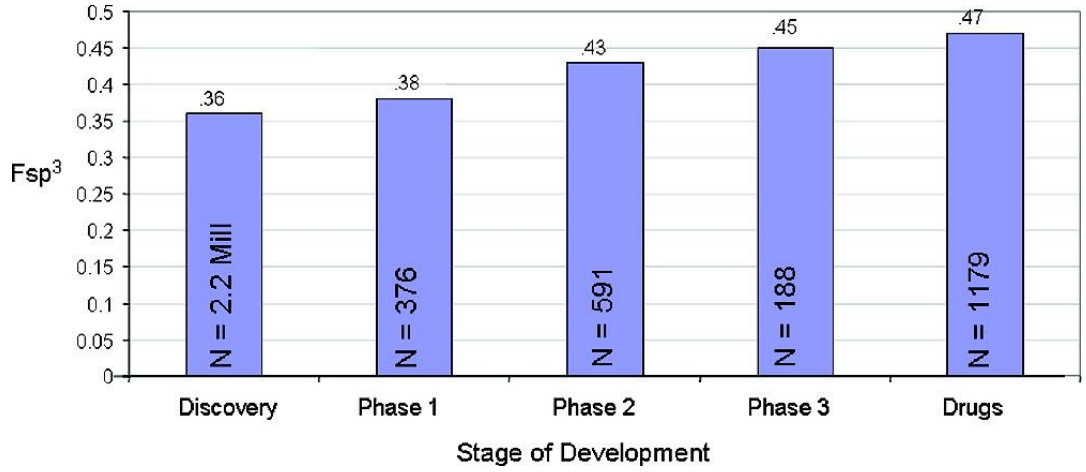


Figure 1: Average Fsp^3 of compounds moving through the stages of drug development[2]

Increased complexity has been linked to improved target selectivity and, more recently, Lovering demonstrated that improved selectivity does indeed correlate with increased Fsp^3, illustrated in the graph in Figure 2.[3]

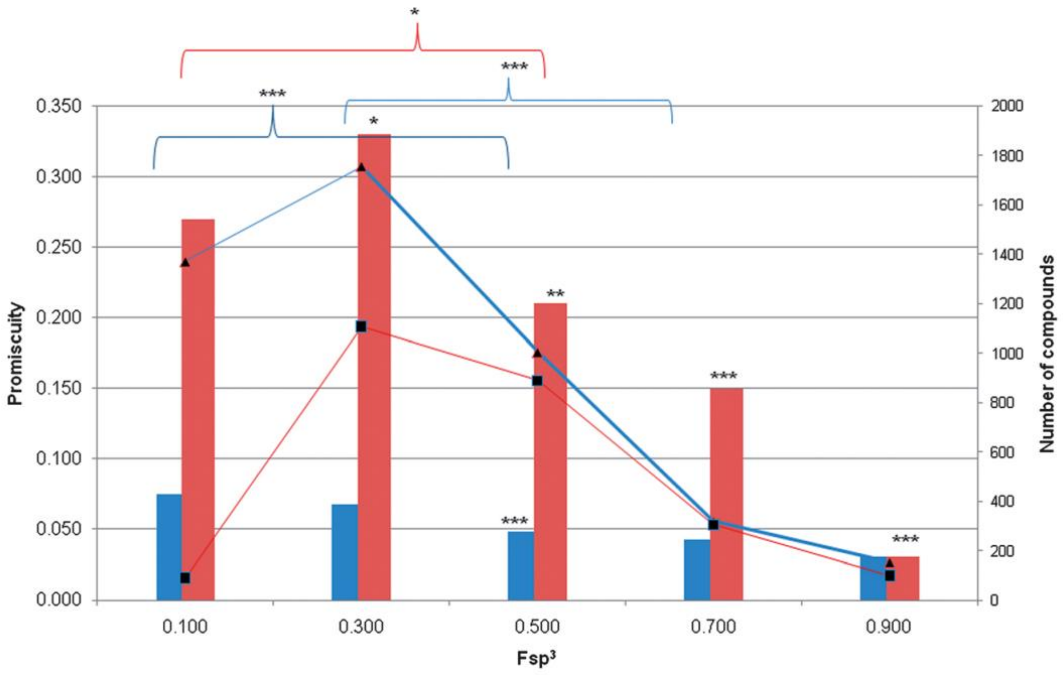


Figure 2: Average promiscuity compared with Fsp³ for compounds [3]

Furthermore, the publication also demonstrates that increased Fsp^3 results in a reduction of the inhibition of Cyp450, an enzyme heavily involved in the metabolism of drug molecules (Figure 3). Avoiding inhibition of this and other anti-targets is an important consideration in modern drug design.

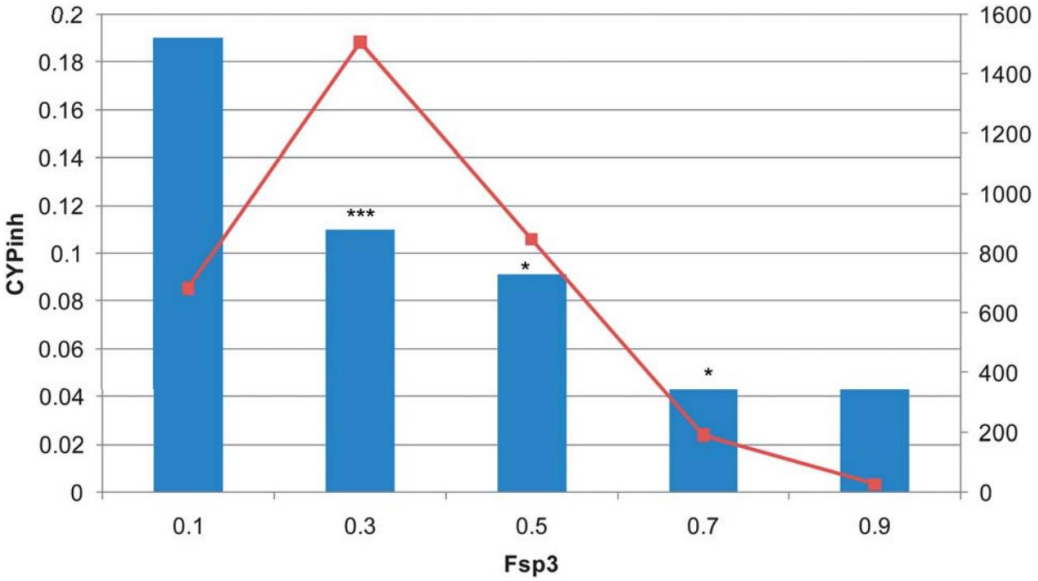


Figure 3: Average Cyp450 inhibition compared with Fsp³ for compounds[3]

1.2 Hydroboration

The first hydroboration of a double bond was achieved fortuitously in the 1950s by Brown and Subba Rao during an investigation into the use of boron hydrides as reducing agents.[4] Whilst performing the reduction of the ester moiety in ethyl oleate (Figure 4) with $NaBH_4$ and $AlCl_3$, it was observed that 2.4 mole equivalents of boron hydride were consumed in the reaction, as opposed to the expected 2 mole equivalents. Examination of the reaction revealed that the boron-hydrogen bond was adding across the alkene, in a reaction which would eventually become one of the most versatile and widely used in organic chemistry.[5]

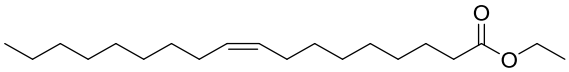


Figure 4: Structure of ethyl oleate

The hydroboration reaction is the *syn*-addition of a boron-hydrogen bond across a carbon-carbon double or triple bond to generate the corresponding organoborane *via* a concerted asynchronous mechanism. Borane reagents have an electrophilic nature, therefore the regioselectivity of the addition provides predominantly anti-Markovnikov products, i.e. the hydrogen adds to the most substituted carbon of the double-bond. The reaction of 'BH_3' will hydroborate more than one equivalent of olefin, generating a trialkylborane as the product; such compounds are particularly unstable to air and moisture so are often subjected to an oxidative work-up to afford the corresponding alcohol.

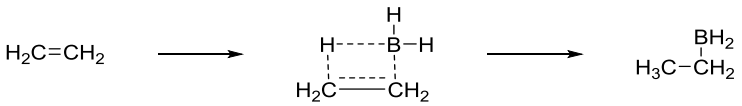


Figure 5: Mechanism of hydroboration reaction

Borane (BH_3) is a gas, and exists in a fast equilibrium with B_2H_6 (most reactions occur with BH_3), as illustrated in Figure 6:

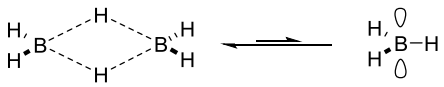


Figure 6: Equilibrium between B_2H_6 and BH_3

BH_3 can be handled as a liquid at low temperatures, however, complexing it with ether (Et_2O), tetrahydrofuran (THF) or dimethyl sulfide (DMS) furnishes a form that is primarily used

within hydroboration chemistry. The vacant orbital in BH_3 can accept a lone pair of electrons from a Lewis base to give a neutral species.

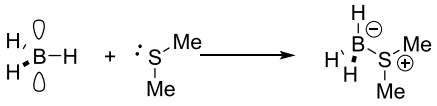
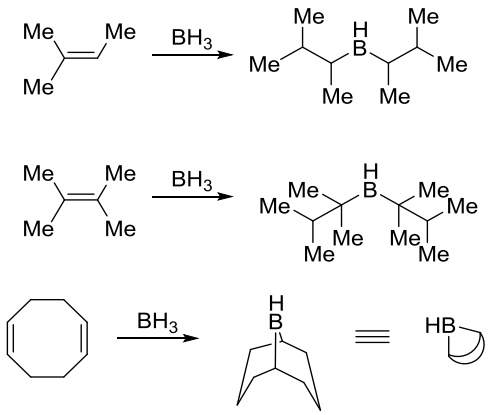


Figure 7: Formation of stable borane species through complexation with DMS

The regioselectivity of the hydroboration reaction becomes rather unpredictable when the substitution pattern of the alkene is not mono-substituted, and the anti-Markovnikov isomer is not always formed. For di-substituted internal alkenes, there is little discrimination in reactions with 'BH_3'. The use of sterically encumbered boranes can circumvent this problem through steric effects, and some commonly used partially alkylated, bulky boranes are disyamylborane, thexylborane and 9-borabicyclo[3,3,1]nonane (9-BBN). These are formed from the hydroboration of 2-methyl-2-butene, 2,3-dimethyl-2-butene and 1,5-cyclooctadiene respectively, as shown in Scheme 3.



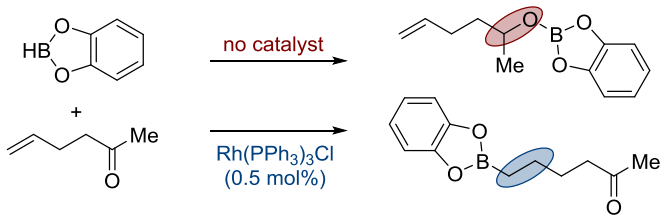
Scheme 3: Synthesis of disyamylboane, thexylborane and 9-BBN

Bulky alkyl boranes also have increased sensitivity to the structure of alkene: terminal alkenes react at a faster rate than internal alkenes, and *Z*-alkenes more rapidly than *E*-alkenes. Exploitation of this knowledge allows for selective hydrobaration of one double-bond in diene- or triene-containing molecules.

1.2.1 Metal-Catalysed Hydroboration Reactions

Over the past 3 decades, the field of metal-catalysed hydroboration has expanded dramatically. As well as increasing the rate of reaction, the addition of metal catalysts has the advantage of being able to alter chemoselectivity and regioselectivity for multifunctional substrates,

compared with that observed for the analogous non-catalysed process. For example, catecholborane adds preferentially to a carbonyl group in the absence of a catalyst, however, when a substoichiometric amount of Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) is added, the hydroboration exclusively occurs on an alkene.[6]



Scheme 4: Hyroboration regioselectivity observed in the presence and absence of Wilkinson's catalyst

The ability of late transition metals to catalyse the hydroboration of carbon-carbon multiple bonds was first exploited by Wilczynski and Sneddon in the early 1980s, in a paper which reports the cobalt-catalysed reaction of dimethylacetylene with pentaborane.[7] Following this, Mannig and Noth produced their seminal publication on the use of catecholborane in hydroboration reactions, in which they rightfully recognise and highlight the vast synthetic utility of the transformation.[8]

Since then, hundreds of novel catalyst systems have been developed, using a variety of different metals, including Zr,[9,10] La,[11] Sm,[12] Ru,[13] Pd,[14] Ni and Ir.[15,16] Rhodium is by far the most commonly employed metal, with iridium being the next most frequently employed. Iridium owes its success to its complementary regioselectivity to rhodium in the hydroboration of vinyl arenes, where iridium gives complete selectivity for the linear isomer.

1.2.2 Rhodium-Catalysed Hydroboration Reactions

Examples of rhodium-catalysed hydroborations prior to the mid-1980s were scarce, but not entirely absent. Indeed, in 1975 Kono and Ito observed the oxidative addition of Wilkinson's catalyst, when treated with catecholborane;[17] Westcott *et al*. subsequently isolated and characterised the tri-isopropyl phosphine equivalent by X-ray crystallography.[18] However, it was Mannig and Noth's landmark paper in 1985 which saw rhodium-catalysed hydroborations to come to fruition, through the use of Wilkinson's catalyst.[8] The reaction between catecholborane and alkenes had been historically very slow, and required elevated temperatures, so this publication presented a real opportunity for the application of hydroboration with catecholborane.

1.2.3 Mechanistic Considerations of Rhodium-Catalysed Hydroboration Reactions

It has been well established that the mechanism of rhodium-catalysed hydroboration differs significantly from the uncatalysed process. The mechanistic pathway is also thought to depend on the nature of the substrate, the catalyst, the ligand used and the reaction conditions employed.[19,20]

In the case of Wilkinson's catalyst, the mechanism is believed to be as follows (Figure 9): dissociation of a triphenylphosphine ligand begins the cycle, to afford the active catalyst species **1**, to which the B-H bond of the borane reagent oxidatively adds. Westcott *et al*. have isolated and structurally characterised an analogous complex (with $P(i\text{Pr})_3$, rather than PPh_3), providing evidence for the formation of this species.[18] Next, complex **2** is formed through the coordination of the alkene *trans* to the chlorine (in the reactive form of this compound, the hydride and the boryl ligand must be *trans* to each other).[21] Migratory insertion of the alkene into the rhodium-hydride bond produces two regioisomeric alkyl boronate esters, which will give the *anti*-Markovnikov and Markovnikov product, following reductive elimination.

This step has been confirmed by Roper and Wright through studies with osmium boryl complexes.[22] It is widely believed that this is the rate determining step, as suggested by Mannig and Noth and subsequently confirmed by Evans and Fu.[23] There has been much debate, however, into whether the reaction occurs through an associative mechanism, or a dissociative mechanism (homologous to the hydrogenation mechanism). Burgess *et al*. believed that the mechanism is associative, and involves a six-coordinate rhodium species,[6] although Dorigo and Schleyer contest this proposal, through the use of *ab initio* studies.[24]

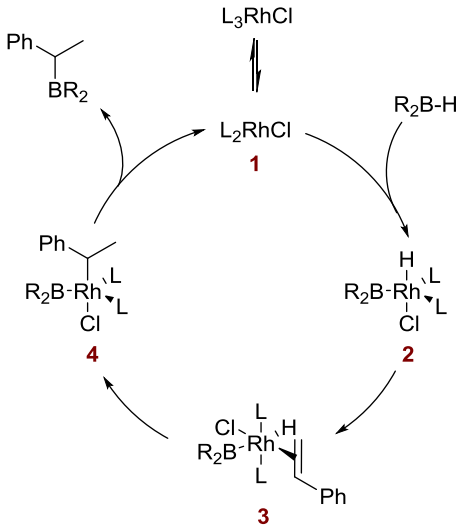
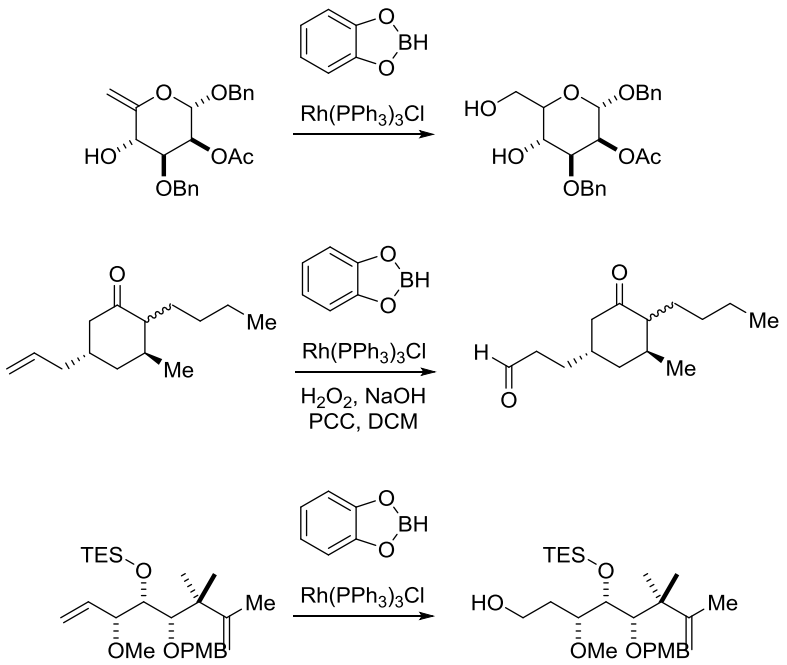


Figure 9: Simplified rhodium-catalysed hydroboration mechanism

1.2.4 Scope of Rhodium-Catalysed Hydroboration Reactions

The substrate scope of rhodium-catalysed hydroboration is relatively large, but the rate of reaction depends heavily on the alkene. Generally, the greater the degree of substitution, the lower the rate of reaction: mono-substitution > 1,1-disubstituted > 1,2-disubstituted >> tri- and tetra-substituted alkenes.[25] The rate decreases to the point where tri- and tetra-substituted alkenes are essentially unreactive under standard catalysed hydroboration reaction conditions.[26]

The reaction has been successfully utilised in a multitude of total syntheses, typically to furnish an alcohol (Scheme 5). For example, in 1996, Cossy used a rhodium-catalysed hydroboration in the synthesis of (+)-ptilocaulin.[27] Boger also showed the application of the reaction to functionalise a cyclic substrate to afford an L-gulose derivative in efforts towards the synthesis of bleomycin A_2.[28] The reaction's excellent chemoselectivity is illustrated in Evans' synthesis of calyculin A, in which the mono-substituted diene is hydroborated exclusively.[29]

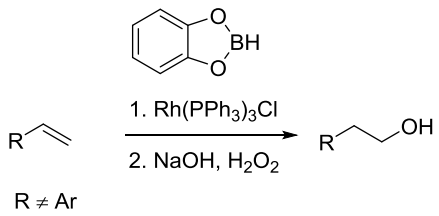


Scheme 5: Examples of rhodium catalysed hydroboration reactions in total syntheses

1.2.5 Regioselectivity in Rhodium-Catalysed Hydroboration Reactions

As discussed above, the uncatalysed hydroboration of an alkene favours the *anti*-Markovnikov product, whilst the catalysed version can be modified to produce either Markovnikov or *anti*-Markovnikov products. It has been shown that metal-bearing ligands greatly affect the regioselectivity of the catalysed reaction, as well as steric and electronic effects.

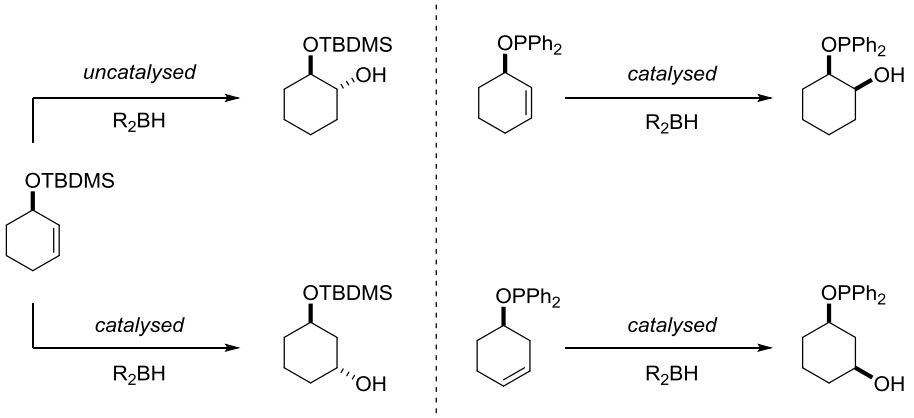
This is not the case for monosubstituted alkenes. Regardless of the absence or presence of catalyst, the *anti*-Markovnikov product is solely obtained (except for vinyl arenes). The catalysed version of this reaction still holds the benefit of being complete often within minutes at room temperature, in comparison to the ~ 90 °C required for the uncatalysed reaction.



Scheme 6: Metal-catalysed hydroboration of monosubstituted alkenes and subsequent oxidation

Functional groups with directing abilities have been shown to control the regioselectivity of metal-catalysed hydroboration reactions. High levels of regioselectivity are observed for the hydroboration-oxidation of *O*-protected cyclohexanols. In the presence of Wilkinson's

catalyst, the *anti*-1,3-diol is the major product formed, whilst in the absence of catalyst, the *anti*-1,2-diol is preferentially formed. It is believed that the selectivity is caused by steric effects, as the *tert*-butyldimethylsilyl (TBDMS) group occupies a pseudo-equatorial position with respect to the cyclohexyl ring. By contrast, in the case of the phosphorus-bearing alkenes in Scheme 7, *syn*-selectivity is observed. It is presumed that the cause of selectivity is coordination of rhodium (which is required in stoichiometric amounts) to the phosphorus site, in a directing group like fashion.[30]

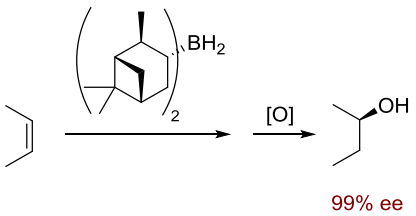


Scheme 7: Directing group selectivity in hydroboration reactions

1.3 Enantioselective Hydroboration Reactions

1.3.1 Metal-Free Enantioselective Hydroboration Reactions

Brown's remarkable publication in 1961, showing the enantioselective hydroboration of simple alkenes with (-)-diisopinocampheylborane [$(Ipc)_2BH$], presaged a new age of asymmetric synthesis.[31,32] At this time, asymmetric chemistry was a domain governed by enzymes and large molecules, however, Brown elegantly exhibited that low molecular weight compounds were capable of achieving excellent levels of enantioselectivity.



Scheme 8: Asymmetric hydroboration with $(Ipc)_2BH$

A range of chiral hydroborating agents have subsequently been developed, but due to the ease of synthesis and wide applicability, $(Ipc)_2BH$ remains broadly used. This reagent has been

applied to the successful synthesis of natural products on numerous occasions, including loganin,[33] prostaglandin derivatives[34] and zeaxanthin (Figure 10).[35]

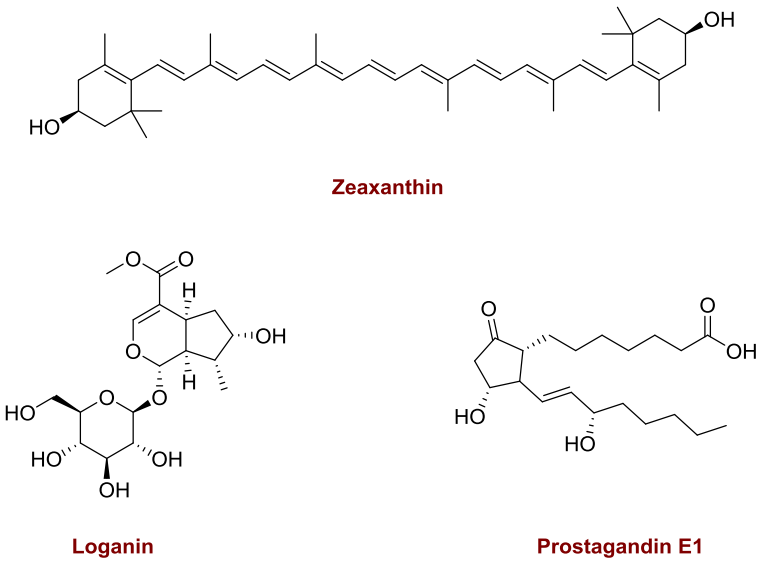
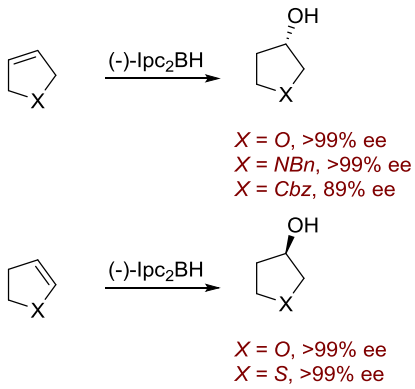


Figure 10: Examples of natural products, whose synthesis has involved the use of $(Ipc)_2BH$

One compelling advantage of $(Ipc)_2BH$ over other hydroborating agents is its simple and economical synthesis. Both enantiomers can be prepared from the commercially available terpene, α-pinene: the most abundant monoterpene in the world.[36] Commercial α-pinene is available in various degrees of optical purity, however it is possible to produce $(Ipc)_2BH$ of higher enantiomeric purity than the α-pinene from which it was derived.[37] This phenomenon is accredited to the preferential amalgamation of the major pinene enantiomer into the crystalline complex, whilst the minor enantiomer accrues in solution.

The first substrate on which $(Ipc)_2BH$ was used was *cis*-2-butene and the resulting product (2-butanol) was achieved with an ee of 87%.[31] In subsequent publications, Brown was able to increase this ee to 99% through an improved method of synthesis of $(Ipc)_2BH$, which works exceptionally well for the hydroboration of mono substituted *cis*-alkenes. Extraordinary regio- and enantio-selectivity is also observed for heterocyclic alkenes (Scheme 9).



Scheme 9: Hydroboration of heterocyclic alkenes using (-)-Ipc$_2$BH

The optical purity achieved decreases notably with increasing steric requirements of the alkene, which presents severe limitations on the scope of the molecules amenable to asymmetric hydroboration.

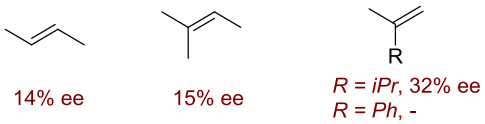
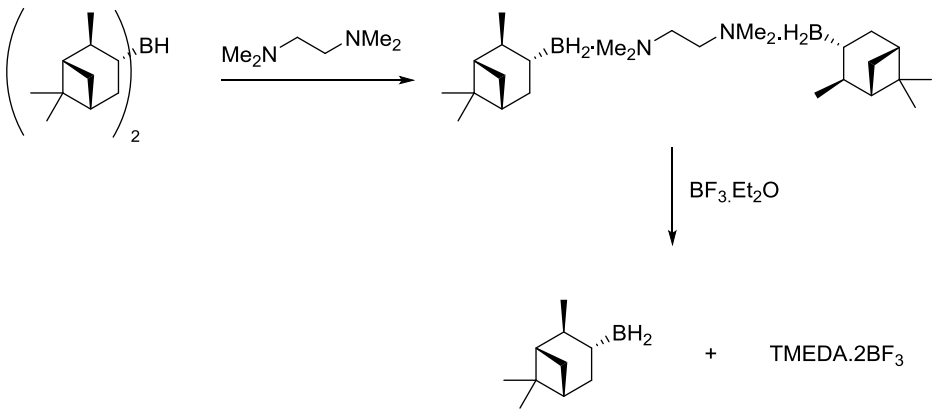


Figure 11: Limitations of hydroborations using (-)-Ipc$_2$BH

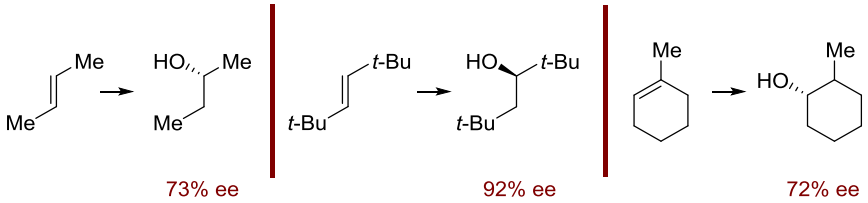
A series of monoalkylboranes have been derived to circumvent the problems associated with (Ipc)$_2$BH and the hydroboration of hindered alkenes. Monoisopinocampheylborane (IpcBH$_2$) is more capable at hydroborating hindered alkenes, including tri-substituted alkenes due to the decreased steric requirements.[38]

The synthesis of IpcBH$_2$ is not quite as straightforward as its dialkylborane counterpart (Scheme 10). Stoichiometric control (i.e. one equivalent of 'BH_3') produces a mixture of mono- and dialkylborane. Instead, (Ipc)$_2$BH is treated with tetramethylethylenediamine (TMEDA) to generate a dimer as a crystalline solid with 100% ee. The subsequent addition of BF_3.Et_2O affords two equivalents of IpcBH$_2$.



Scheme 10: Synthesis of IpcBH$_2$

IpcBH$_2$ has been successfully employed to hydroborate a multitude of sterically encumbered and tri-substituted alkenes, alleviating the limitations of (Ipc)$_2$BH. From the results shown in Scheme 11, it appears that increasing the steric bulk of alkene improves the optical induction achieved in hydroborations with IpcBH$_2$. This complementary reactivity means that together, (Ipc)$_2$BH and IpcBH$_2$, can accommodate three out of the four major alkene subgroups.



Scheme 11: Enantioselective hydroboations of substituted alkenes

Derivatives of IpcBH$_2$ - mono(ethylapoisopinocampheyl)borane (EapBH$_2$)[39] and mono(phenylapoisopinocampheyl)borane (PapBH$_2$)[40] - have since been developed. Their syntheses do not begin with commercially available alkenes and as such, their synthetic utility is severely reduced.

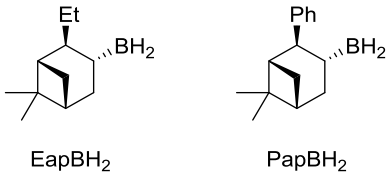


Figure 12: Structures of EapBH$_2$ and PapBH$_2$

The chiral hydroborating agents discussed are by no means an exhaustive list. One notable addition is Masamune's *C*$_2$-symmetric borane, 2,5-dimethyl borolane (DMB).[41] For many substrates, DMB exceeded Brown's reagents, however, the cumbersome seven-step synthesis reduces its practicality and general use.

1.3.2 Metal-Catalysed Enantioselective Hydroboration Reactions

A noteworthy milestone in the advancement of metal-catalysed hydroboration is the development of an asymmetric variant of the reaction. The application of this reaction expands through a broad range of chemistry, with the most common utilisation being in the formation of enantiomerically enriched alcohols through oxidation of the alkylborane intermediate.[42] There have been two main approaches to gaining enantioselectivity in metal-catalysed hydroborations, the first of which involves the use of a chiral hydroborating agent and an achiral catalyst, pioneered by J. M. Brown in 1990.[43] This method achieved encouraging levels of enantiomeric excess but poor regiochemical control severely restricted the reaction. Also, the addition of chiral ligands had little effect on the enantiomeric excess gained.

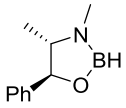


Figure 13: Chiral oxazaborolidine borane used by Brown *et al.*

The more common approach is the reverse of this: a chiral catalyst system and an achiral borane source. This technique was established by Burgess,[44] Suzuki[45] and Hayashi,[46] and makes use of chiral diphosphine ligands which have previously been used in other asymmetric processes. It was the work of Hayashi which truly proved that high levels of entioselectivity were accessible, however. His studies used BINAP as the chiral ligand (to this day, BINAP remains one of the most successful ligands for asymmetric metal-catalysed hydroborations) and a selection of styrenes were examined. Electron-rich styrenes with little steric hindrance achieved the highest enantioselectivities, although β-methylstyrene derivatives reacted with poor enantioselectivities, due to their reduced reactivity and thus higher reaction temperatures necessary.[47]

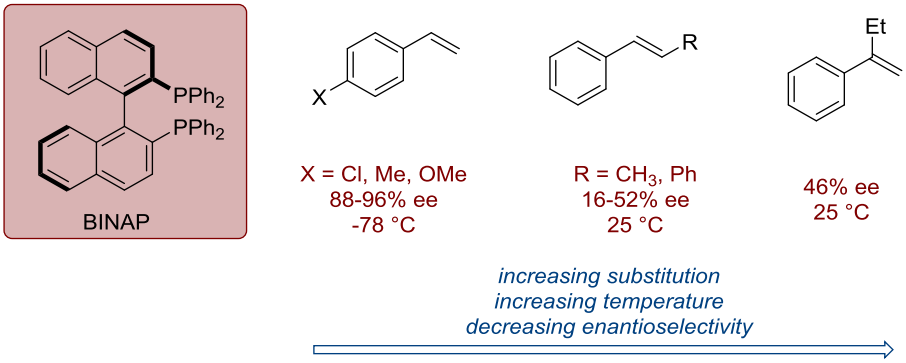


Figure 14: Enantioselective hydroborations with [Rh(COD)BF_3] and BINAP with general trend shown

A palette of other diphosphine ligands have been shown to be successful at inducing asymmetry in metal-catalysed hydroborations as displayed in Figure 15. It is perhaps surprising that, despite its well precedented success and continuing achievements, there have been so few BINAP analogues reported within this reaction manifold.

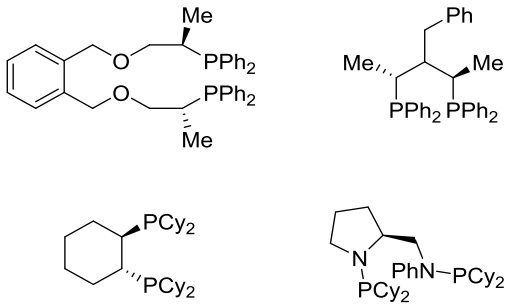


Figure 15: Examples of diphosphine ligands which have been used in enantioselective hydroborations

The other ligand type used in asymmetric hydroborations is phosphinamine ligands. J. M. Brown founded this application with the use of QUINAP.[48] Unlike BINAP, QUINAP is capable of generating asymmetry at ambient temperatures, allowing sterically hindered or unreactive substrates to be hydroborated enantioselectively (Figure 16). As listed previously, electron-rich substrates were hydroborated with higher levels of enantioselectivity. This is a trend which has been explored considerably and several theories have been proposed. Chan *et al*. (who observed the same trend with their use of PyPhos)[49] suggested that electron-rich olefins bind more tightly to cationic rhodium and thus the substrate is more strongly affected by its chiral environment.

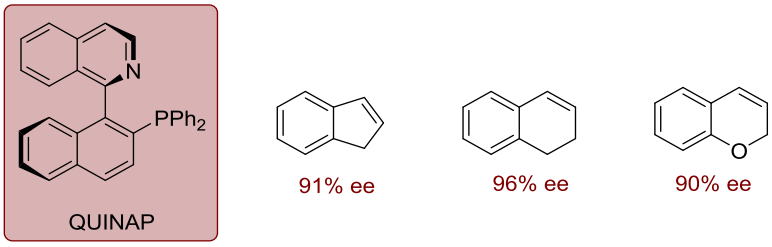


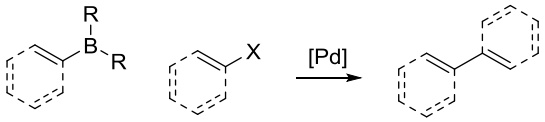
Figure 16: Structure of QUINAP and selected examples

So far, the biggest caveat with enantioselective metal-catalysed hydroboration is the substrate scope. The majority are only effective on vinyl arene substrates; a ligand which can achieve high levels of asymmetry and regioselectivity on a wide range of substrates remains elusive.

1.4 Suzuki-Miyaura Cross-Coupling Reaction

1.4.1 Introduction to the Suzuki-Miyaura Reaction

Since its discovery in 1979,[50] the Suzuki-Miyaura (SM) cross-coupling has become one of the most widely used reactions in the chemical industry, forming carbon-carbon bonds *via* the palladium catalysed cross-coupling of an organoborane species with an organohalide or pseudohalide.



Scheme 12: Generalisation of the SM reaction

In 2010, Akira Suzuki was awarded the Nobel Prize in Chemistry for his contributions to the field of cross-coupling; an honour he shared with Richard Heck and Ei-Ichi Negeshi. The SM reaction is used extensively in a breadth of chemistry disciplines, including polymer chemistry,[51] process chemistry,[52] natural product synthesis[53] and medicinal chemistry. Indeed, a comprehensive survey of the pharmaceutical industry found that the SM reaction was responsible for more than 40% of all carbon-carbon bond forming reactions.[54]

The popularity of the SM reaction is certainly not incidental, and the preference of this reaction over other transition metal (TM)-catalysed cross-couplings can be attributed to several factors. Key advantages include relatively mild reaction conditions, a broad choice of commercially available starting materials and the tolerance of the reaction to an extensive range of functional groups. The organoborane groups employed are non-toxic and environmentally safe, especially when compared with those used in other TM-catalysed cross-coupling reactions (e.g. Kumada, Stille, Negishi, etc.) Additionally, these factors make the task of scale-up relatively facile.

Over the past three decades, the SM reaction has received continual attention and a significant number of publications have added to and expanded the ever-growing scope of the reaction. One aspect of the process which has been investigated scrupulously is the mechanism. A generalised catalytic cycle is shown below in Figure 17. This is universally believed to be the mechanistic pathway of the reaction, though differences within each step have been extensively debated, particularly in recent years.[55]

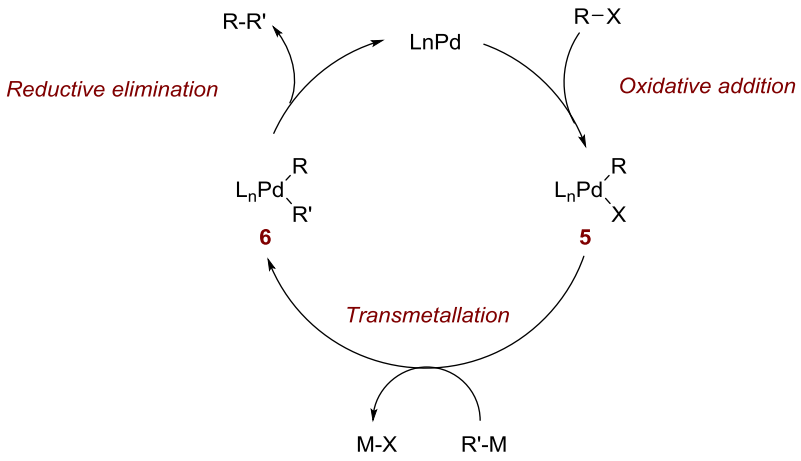


Figure 17: Generalisation of the SM reaction catalytic cycle

1.4.2 Mechanistic Considerations with the Suzuki-Miyaura Reaction

Mechanistically, the reaction begins with oxidative addition, which gives rise to an organopalladium (Pd^{II}) complex (**5**) by the addition of Pd into the carbon-halogen bond. The intermediate formed is initially *cis* but rapid isomerisation gives the *trans* isomer.[56] Often, this step is the rate-determining step and the rate is directly correlated to the type of halogen/psuedohalogen in a general reactivity pattern of I > OTf > Br >> Cl. Bromides, however, are the most commonly employed halogen due to their commercial availability. Other aspects of the reactions can be altered to influence the rate of this step, for example, an electron-deficient organohalide will increase the rate, as will the use of an electron-rich ligand. It has been shown that oxidative addition occurs with retention of stereochemistry for vinyl halides, but with inversion of stereochemistry for alkyl halides or benzyl halides (this has been debated recently, though).[57]

The second step in the catalytic cycle is transmetallation, and it is the stage which has been subject to most discussion in recent years. In order for efficient transfer of the organic moiety from an organoboron species to the Pd centre, the three-coordinate boron species must become a four-coordinate "ate" complex, by association of a fourth ligand. It is the origin of this fourth ligand that has been under scrutiny.

The two proposals can be divided into two mechanistic classifications: the boronate pathway and the oxo-palladium pathway. The former pathway dictates that the boronate species is formed before associating with the intermediate, through the reaction with hydroxide anion (**7**). The latter pathway involves the formation of an oxopalladium intermediate (**8**), so the

necessary four-coordinate species is only formed consequent of coordinating with Pd. Both pathways are depicted in Figure 18.

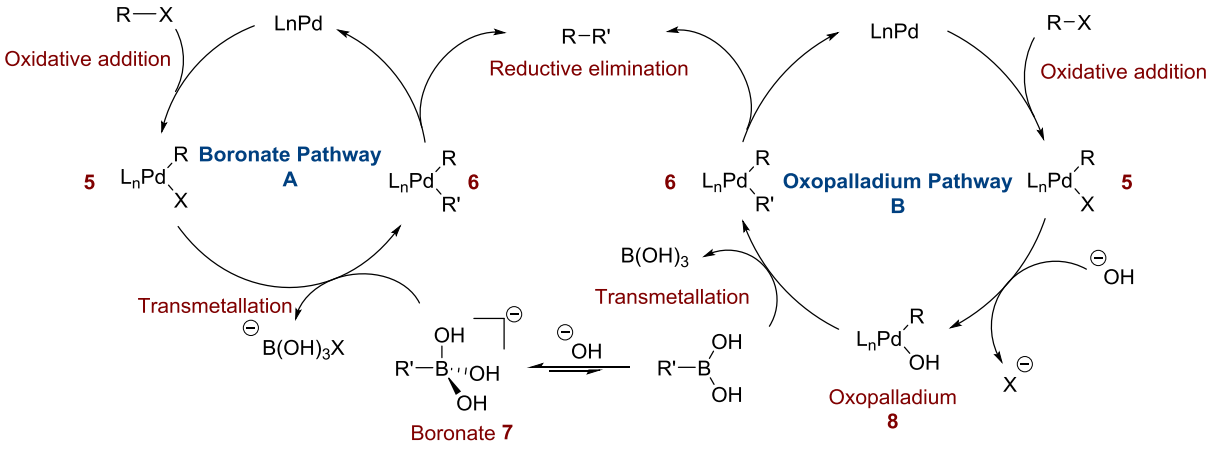


Figure 18: Boronate pathway vs oxo-palladium pathway in the SM reaction

It was concluded that the initial failure in attempts to cross-couple organoboron reagents with organo halides, prior to Suzuki's pivotal publication, were due to the lack of nucleophilicity of the organoboron reagents.[58] This was a reasonable deduction as the addition of NaOEt and NaOH (which was thought to convert the organoborane reagent to a four-coordinate 'ate' complex) resulted in a successful cross-coupling reaction.[59] However, several years later, a study on alkenyl-alkenyl cross-coupling displayed evidence of the oxo-palladium pathway, and thus caused opinion to vacillate.[59]

Since then, research into the elucidation of the dominant pathway has flourished. A series of computational[60] and kinetic studies,[61] along with the preformation and reaction of the proposed boronates,[62] have shown considerable evidence in favour of the oxo-palladium catalytic transit. Indeed, the work of Hartwig,[63] Lloyd-Jones, Amatore and Jutand[64] has provided almost conclusive proof to confirm this. This certainty is only true for specific boronic species and simple aryl halides, however, and ambiguities still exist, for example, in the possibility of the pathways to evolve from B to A, or *vice versa*. On the contrary, there is a scarce amount of substantial evidence to suggest that path A is the prevailing reaction manifold.

The final stage of the pathway is reductive elimination: this involves the release of the desired product as well as the regeneration of Pd^0. Excluding a few exceptions, the ligands must be *cis* to each other to reductively eliminate (*trans* complexes have been observed to isomerise to *cis*). An augmented rate is observed with *p* character: $sp > sp^2 > sp^3$. Since reductive elimination can be described as the microscopic reverse of oxidative addition,[65] many of the reactivity

trends for oxidative addition are the opposite of those for reductive elimination. For example, electron deficient ligands increase the rate of this step, as this provides a more electron poor metal centre which is more disposed to accepting electrons (a requirement of this step). Sterically hindered ligands are also favourable for reductive elimination: the energetic driving force is the relief of strain within the metal complex. A bulky ligand will increase the extent of strain associated with the initial complex, making the energy drop accompanying this step greater.[65]

1.4.3 Boron Species Used in the Suzuki-Miyaura Reaction

Neutral boron has three outer-shell bonding electrons ($2s^2$, $3p^1$), which can participate in three sp^2 bonds, conferring a trigonal planar geometry. Orthogonal to the plane lies a non-bonding *p*-orbital, making boron compounds liable to electron donation. As discussed before (with regards to the oxo-palladium pathway of transmetallation), coordination to boron compounds can create tetrahedral 'boronates' which possess disparate properties to their trigonal planar counterparts. The boron reagents employed in the early stages of the SM reaction were alkenyl boranes and catechol boronic esters, which were relatively quickly replaced by boronic acids. Over the past few years, the development of novel boron reagents has thrived and a multitude are currently available with differing stabilities and reactivities which have extended the scope of the reaction. In 2010, Mayr developed a scale to determine the relative nucleophilicity or electrophilicity of a vast range of compounds,[66] and this was extended in 2012 to compare the reactivities of the most commonly used boron species[67] (Figure 19).

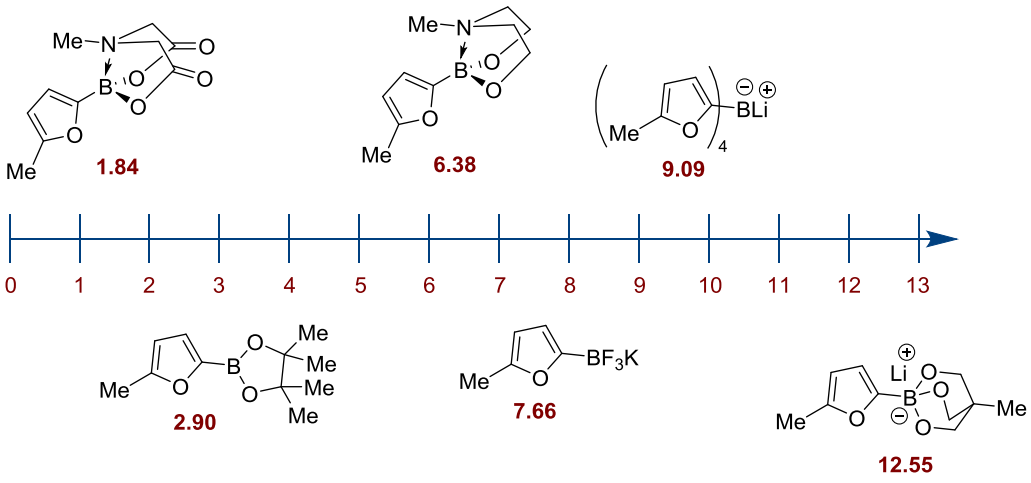
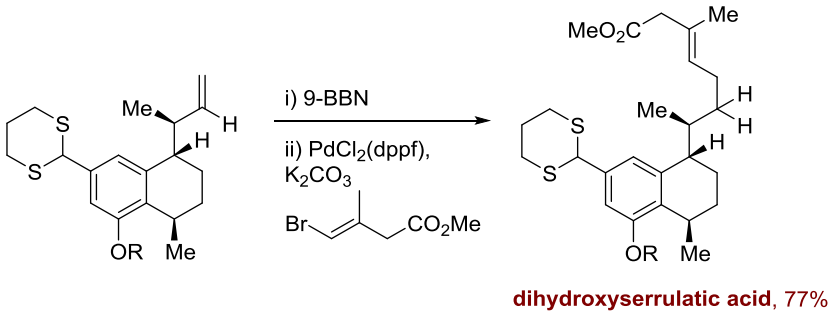


Figure 19: Mayr's nucleophilicity scale for commonly employed boron reagents[67]

1.4.3.1 Organoboranes

One of the first boron species to be used was organoboranes, due to their ease of synthesis. The choice of alkyl ligand on theorane is key: there must be adequate differentiation between the 'R' groups in trialkyl boranes so that the transmetallation step is selective.[68] 9-BBN has been shown to have the greatest degree of selectivity compared to other trialkylboranes. Organoboranes have a tendency towards aerobic oxidation, which heavily limits their utility, as well as lowering reaction yields if conditions are not completely anaerobic. Protodeboronation has also been exhibited to occur in alcoholic solvents, with 9-BBN having the highest rate.[69]

Despite their propensity to a variety of unfavourable side-reactions, organoboranes have frequently been employed in SM reactions. An example of a two-pot hydroboration-SM reaction is shown below in the synthesis of dihydroxyserrulatic acid, in which an alkyl-alkenyl cross-coupling takes place.[70]



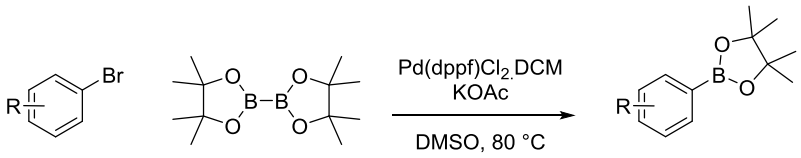
Scheme 13: Syntheisis of dihydroxyserrulatic acid using an organoborane

1.4.3.2 Boronic Esters

Boronic esters have played an important role in the history of boron chemistry – most metal-catalysed hydroborations are performed using catecholborane, the products of which have been successfully used in SM reactions. Catechol-boronic esters have been shown to have relatively low stability, though, due to a decreased π-donating ability of oxygen to boron (this is attributed to competing conjugation with the phenyl ring).[71] Consequently, pinacol- or neopentyl-boronic esters are the more frequently used boronic esters, owed to their ease of synthesis and increased stability. The active transmetalating species during SM reactions remains unclear when boronic esters are used, however. Two possibilities exist: a) the boronic ester reacts with an oxo-palladium intermediate or b) hydrolysis of the boronic ester occurs to form the corresponding boronic acid which goes on to react through either of the two

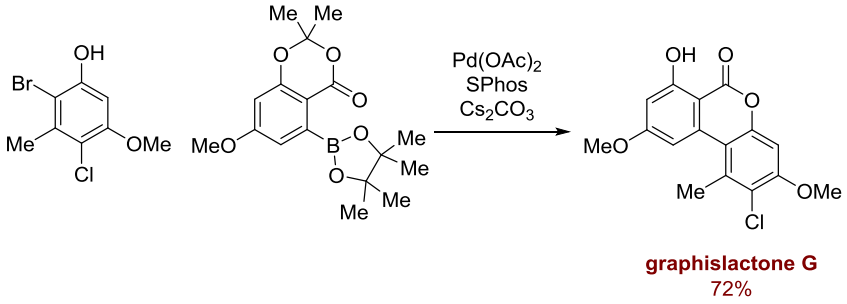
transmetallation pathways previously discussed. Water-free SM coupling boronic esters have been published,[72] though the chance of adventitious water being present is certainly possible.

Typical syntheses of boronic esters include hydroboration of alkenes or alkynes, or Miyaura borylation. Miyaura developed the palladium catalysed reaction of an aryl[73,74] or alkenyl halide[75] to a boronic ester in the 1990s, representing a mild route into these useful intermediates. The reaction follows a similar mechanistic manifold to the SM reaction, through a Pd(0)/Pd(II) pathway. Choice of base is very important – typically, a weak base (such as KOAc) is used to avoid the coupling of starting aryl halide and the resultant boronic ester.



Scheme 14: General reaction conditions for Miyaura borylation

Other, less common methods of boronic ester synthesis include a Sandmeyer reaction based protocol,[76] electrophilic arene borylation[77] and the use of Grignards or organolithium reagents. An example of boronic esters being used in the synthesis of graphislactone G is shown below.



Scheme 15: Synthesis of graphislactone G using a boronic ester[78]

1.4.3.3 Boronic Acids

Boronic acids were first employed as coupling partners very early in the SM reaction timeline. Their first reported use was just two years after the first report from Suzuki, in 1981,[79] and they remain a widely used boron species due to the large commercial availability and high atom economy. In solution, equilibrium exists between the boronic acid and the corresponding boroxine (formed from the loss of three water molecules). To account for this dehydration, an excess of boronic acid is often added.

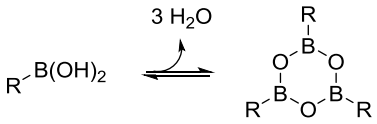
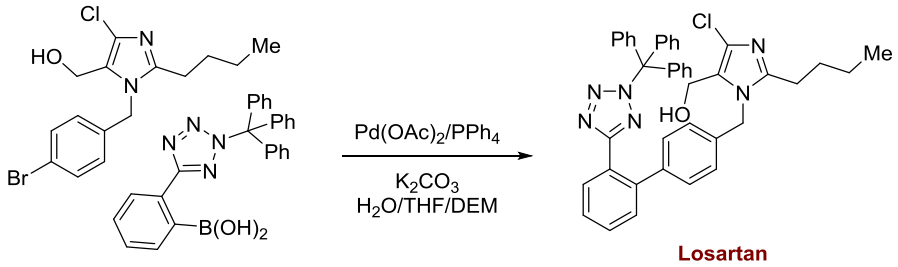


Figure 20: Equilibrium between boronic acid and boroxine

One of the foremost disadvantages is the tendency of certain boronic acids to protodeboronate. This is of particularly concern when kept out of solution, as recent studies have shown certain boronic acids are less prone to protodeboronation in solution.[80] Other problems associated with their use include oxidation and palladium-catalysed homo-coupling.[81]

Many of the methods of synthesis are similar to that of boronic esters, for example, the reaction of Grignard or organolithium reagents with a boric ester,[82,83] a Miyaura borylation (with tetrahydroxydiboron instead of B_2pin_2),[84] or indeed the hydrolysis of boronic esters.[85] The scheme below shows an application of boronic acids in a SM reaction, for the commercial synthesis of hypertension drug, Losartan.



Scheme 16: Synthesis of Losartan using a boronic acid in SM coupling[86]

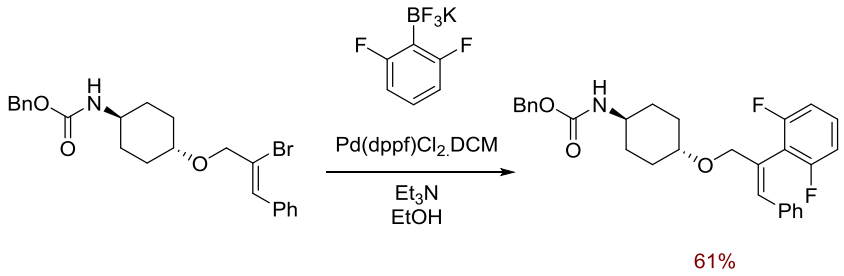
1.4.3.4 Potassium Organotriflouroborate Salts (BF_3K)

In 1960, Chambers *et al.* first reported the formation of potassium organotrifluoroborate salts (R-BF_3K) through a displacement reaction of tin,[87] but publications regarding their use were scarce in the subsequent thirty years. It was not until the 1990s that their importance and function was deservedly acknowledged and, since then, they have become an increasingly common and widely used functionality. All the aforementioned species of boron compounds possess an empty *p*-orbital on boron, rendering them vulnerable to oxidants, bases, nucleophiles, etc. The organotrifluoroborate species, however, are four-coordinate in nature, making them a superior alternative in terms of stability, and as a functional handle that can be carried through a variety of synthetic steps.

It was not until 1995 that a safe, robust method of synthesis was developed, and this was achieved by Vedejs through the use of potassium bifluoride (KHF_2).[88] Boronic acids were

treated with a saturated aqueous KHF_2 solution and the corresponding BF_3K salts were attained in good yields. The availability of boronic acids makes the scope of this reaction very broad.

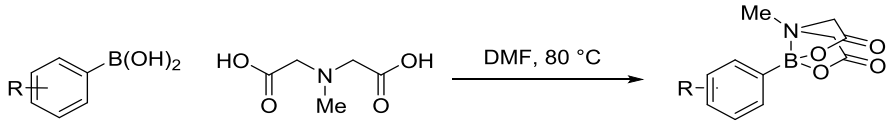
As stated above, throughout the last decade particularly, BF_3K salts have been used extensively. Their increased shelf-life, lower susceptibility to protodeboronation and, in some cases, increased reactivity make them a strong choice of boron species for SM reactions. Scheme 17 illustrates the employment of an aryl BF_3K salt in the synthesis towards an NMDA/NR2B antagonist.[89]



Scheme 17: Example of BF_3K used in the synthesis of NMDA/NR2B antagonist

1.4.3.5 Other Boron Species

There exists a large range of boron species capable of acting as a coupling partner for SM reactions, many of which are in their infancy. A subset which fall into such a class are *N*-coordinated boronates, which are categorised by a cyclic boronic ester backbone encompassing a nitrogen atom. The most prevalent ligands within this group are diethanolamine, *N*-methyldiethanolamine, *N*-phenyldiethanolamine and *N*-methyliminodiacetic acid (MIDA). They are bench stable,[90] easily synthesised[90] and recently have found particular importance in iterative SM cross coupling.



Scheme 18: Synthesis of MIDA boronate from boronic acid

1.5 sp^2-sp^3 Suzuki-Miyaura Coupling Reactions

In comparison to the standard sp^2-sp^2 SM reaction, the sp^3-sp^2 equivalent is in its early stages of development. The cross coupling of an alkyl borane and an aryl or vinyl halide (or *vice versa*) fills a growing niche in the chemical industry, allowing direct access to a plethora of useful molecules.

1.5.1 Coupling of Primary Alkyl Boron Species

Initial work by Suzuki and Miyaura[91] was performed using alkylboranes, substrates which are afflicted by a host of drawbacks: they are air and moisture sensitive; generally, they must be synthesised *in situ*, and as such, there are very few commercially available.

Scheme 19: Initial coupling of alkylboranes with aryl halides

In 1989, Suzuki and Miyaura presented an extension of this work, displaying the coupling of alkylboronic esters with aryl bromides and aryl iodides.[92] Although this work had the advantage of the use of more stable boronic esters, Tl_2CO_3 was used as the base. The toxicity associated with this made the reaction unable to be applied to an industrial setting. These preliminary results were followed by promising improvements, including the replacement of Tl_2CO_3 with CsF by Wright *et al.*,[93] albeit with slightly decreased yields.

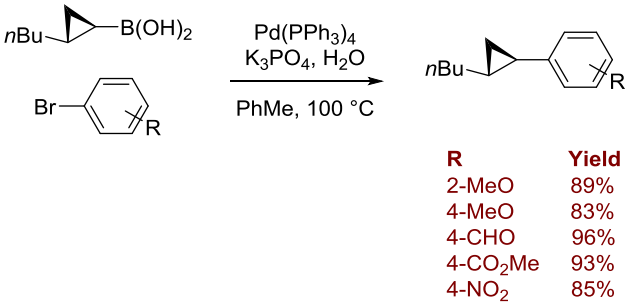
Since its first exemplification, the sp^2-sp^3 coupling process has undergone some substantial development. A relatively wide range of catalysts and mono-, bi- and tetra-dentate ligands have been successfully employed (as low as 0.01 mol%), with aryl bromides and iodides being the most common coupling partner. Elevated temperatures are normally required, often as high as 130 °C.

1.5.2 Coupling of Secondary Alkyl Boron Species

While SM cross-coupling reactions with primary alkyl boronic acid derivatives have been explored for the past two decades, examples of the use of secondary alkyl boron species have remained elusive until recent years. This is probably due to the even slower rates of transmetallation with palladium associated with these congested substrates. The majority of early examples of such reactions, however, were performed with cyclopropylboronic acid derivatives, due to their unique hybridisation which gives partial aromatic character the C-B bond.[94] The coupling of secondary alkyl boron species is of particular interest to the current study (*vide infra*).

The first example of this reaction was performed by Marsden and Hilderbrand in 1996, where they showed the coupling of cyclopropyl boronates with a series of aryl bromides.[95] Later that

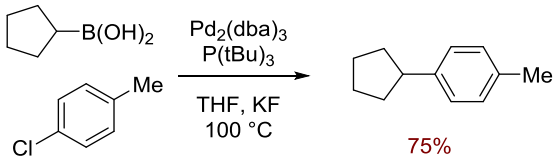
year, Deng and Wang presented a similar protocol but with cyclopropyl boronic acids, showing a wider range of substrates and higher yields.[96]



R	Yield
2-MeO	89%
4-MeO	83%
4-CHO	96%
4-CO_2Me	93%
4-NO_2	85%

Scheme 20: Substrate scope of Deng and Wang's work on the cross-coupling of cyclopropyl boronic acids

Subsequent years saw a variety of coupling reactions which employed cyclopropyl derived boron species,[97,98,99] but other secondary boronic acid derivatives remained scarce. One of the first cases involved the coupling of cyclopentylboronic acid with 4-chloro-toluene by Fu *et al.* (Scheme 21).[100]



Scheme 21: SM coupling of cyclopentylboronic acid and 4-chloro-toluene

In 2008, Molander *et al.* reported a study which aimed to find a 'general solution to the challenge of cross-coupling secondary organometallics'.[101] They employed potassium trifluoroborate salts, in order to circumvent the problems associated with a reduced rate of transmetallation (potassium trifluoroborate salts have been shown to undergo transmetallation with a significantly lower degree of protodeboronation).[102] Parallel microscale experimentation was performed with two different electrophilic models (2 chloroanisole and 3-chloropyridine) in an attempt to achieve conditions suitable for a wide range of coupling partners. The optimum reaction conditions proved successful for cyclohexyl trifluoroborate and a wide variety of aryl chlorides. This was the second example of the coupling of a cyclohexyl group using boron reagents.[103]

Later in the same year, Molander *et al.* presented the coupling of cyclopropyl and cyclobutyl trifluoroborates. Despite the abundance of cyclopropyl coupling, this was the first example of a cyclopropyl trifluoroborate coupling, as well as the novel employment of aryl chlorides in this reaction.

1.5.3 Experimental Considerations for sp^2-sp^3 Suzuki-Miyaura Reactions

Initial studies showed that $Pd(dppf)Cl_2$ and $Pd(PPh_3)_4$ were the most suitable catalysts for *B*-alkyl SM reaction[91,92] and much of the work performed involved complexes with an electron rich Pd^0 centre. One of the biggest mechanistic problems associated the coupling of *B*-alkyl compounds is the tendency of the alkyl-palladium complex to undergo β-hydride elimination, rather than reductively eliminate.

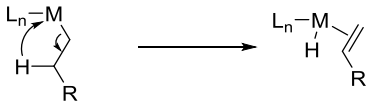


Figure 21: Mechanism of β-hydride elimination

$Pd(dppf)Cl_2$ has been shown to favour reductive elimination by forcing a *cis* geometry on the Pd^{II} complex between the vinyl and alkyl groups. If the reductive elimination step is the rate determining step, this catalyst therefore would prove most effective. Moloy and co-workers have shown that the bite angle of bidentate ligands plays a significant role in catalyst effect.[104] In general, the larger the bite angle, the higher the rate of reductive elimination, due to the two alkyl groups on the Pd^{II} centre being forced closer to each other. Reductive elimination is not the only step affected by catalyst - Buchwald *et al.* have shown the increase in rate of oxidative addition through ligand control.[105,106]

Base and solvent play an imperative part in the success of *B*-alkyl SM reactions and have a complex underlying relationship that is particularly relevant in the context of transmetallation. It has been found that weaker bases (K_2CO_3 and K_3PO_4) work well with solvents like DMF, whereas stronger bases (NaOH and NaOMe) perform superiorly in THF and H_2O.

1.5.4 Stereoselective Suzuki-Miyaura Reaction

It is often very difficult to accurately predict the effect that small steric or electronic alterations can have on the level of asymmetry achieved when employing chiral catalysts. Small modifications to substrates can have large detrimental effects on enantioselectivity, and as such, a lack of generality is commonly seen within this field of chemistry. To bypass this problem, with regards to metal-catalysed cross-coupling reactions, many research groups have developed methods to react optically active alkylboron reagents. The reaction conditions established aim to preserve the stereochemical integrity of the starting material, facilitating a universal reaction which is autonomous of the perturbations discussed above.

This method of achieving a stereogenic centre is still not a straightforward proposition. With all cross-coupling reactions with alkyl organometallic nucleophiles, there is susceptibility for β-hydride elimination to give an olefin product following reductive elimination. Palladium hydride can reinsert into the coordinated alkene, which can induce racemisation.

A further level of complexity is added to the reaction because of the inverse relationship between the nucleophilicity of organometallic nucleophiles and their configurational stability. Covalent character generally coincides with configurational stability, but its relationship with nucleophilicity is antithetical, meaning a balance must be established.

Despite extensive examples showing that SM cross-coupling reactions with α-chiral alkyl boron compounds occur with retention of stereochemistry,[107,99,108] recent publications have shown certain substrates to exhibit inversion of stereochemistry.[109,110] A common feature in the invertive examples is the presence of amide or ester functional groups, which are thought to play an important role in the transmetallation step through coordination.

1.5.5 Mechanistic Considerations for Stereoselective Suzuki-Miyaura Reactions

Each step of the SM reaction has been studied comprehensively, particularly from the perspective of stereoselective sp^2-sp^3 coupling, and the stereochemistry of each step has been considered to fully understand the mechanistic basis of the process. Oxidative addition of alkyl and alkenyl halides occurs with retention of configuration, whilst oxidative addition of benzyl and allylic halides occurs with inversion. The stereochemical outcome of transmetallation is, however, rather more nebulous. It has been suggested that the stereospecificity is eminently dependent on numerous factors of individual SM reactions. Solvent, ligand, temperature, existence of coordinating groups, steric effects of nucleophiles and several other aspects are thought to affect the outcome of the reaction.[111] There exist two possible mechanisms for transmetallation: S_E2 (open or closed) will result in stereoretention; S_E2 involving the minor bonding lobe of C-B, however, will afford product with inverted stereochemistry.[111] A single electron transfer (SET) pathway will result in racemisation and a loss of stereochemistry.

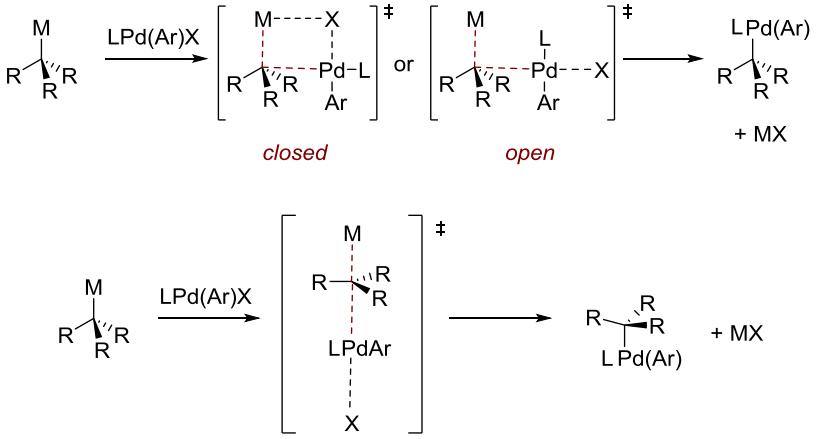


Figure 22: Different proposed transmetalation mechanisms

Soderquist and co-workers claimed that the four-centered hydroxo-bridged transition state model is involved in a stereoretentive transmetalation step.[61] The formation of this is dependent on the Lewis acidity of the organoborane and the idea had been hitherto presented by Suzuki and Miyaura.[112]

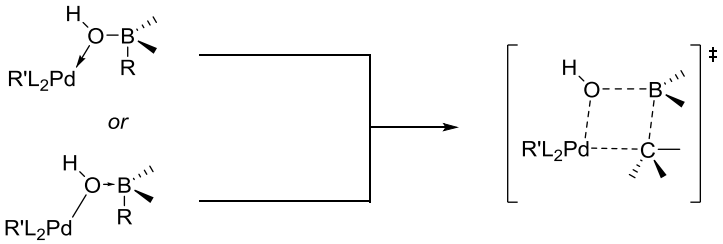
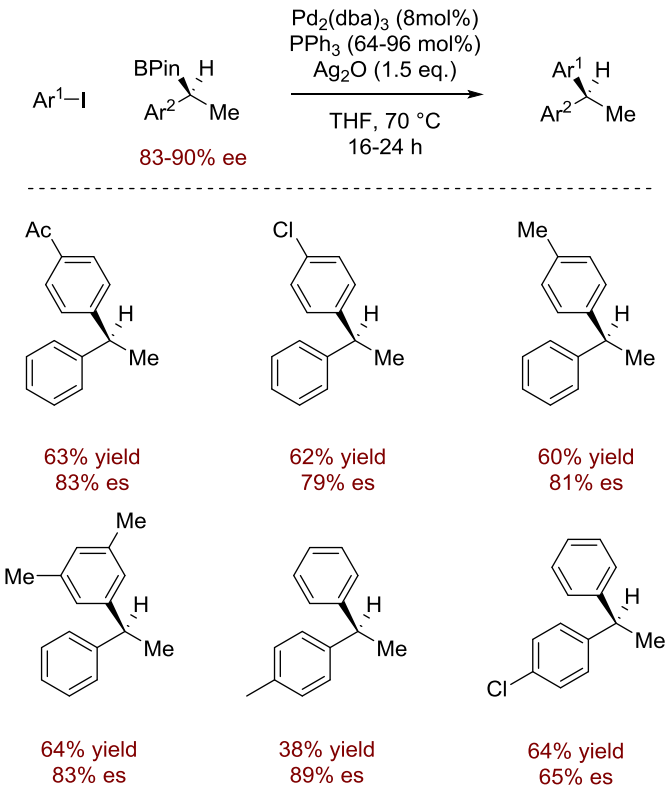


Figure 23: Soderquist's hydroxo-bridged transition state model

An accurate understanding of the mechanistic pathway is vital to the success of stereoselective SM reactions. Further investigation and appreciation of the mechanism will bring additional, more applicable, exemplification of the reaction manifold.

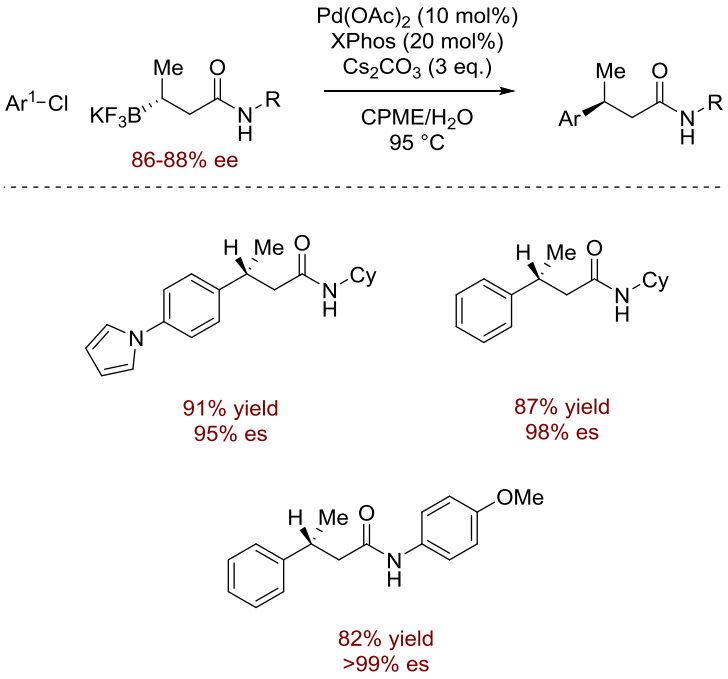
1.5.6 Examples of Stereoselective Suzuki-Miyaura Reactions

Crudden presented the first example of stereospecific Pd-catalysed SM reactions using benzylic organoboronic esters in 2009.[108] Ag(I) was added in stoichiometric levels (to encourage the formation of cationic Pd(II) intermediates) and retention of absolute stereochemistry was shown. The scope, which is limited to electron-deficient and electron-netural iodides, is shown in Scheme 22. High silver and phosphine loadings detract from the allure of this methodology, however. The substrate scope has since been expanded to include dibenzylic nucleophiles, which proceed with greater levels of enantiospecificity (es) than the original scope.



Scheme 22: Substrate scope of the first reported stereospecific SM

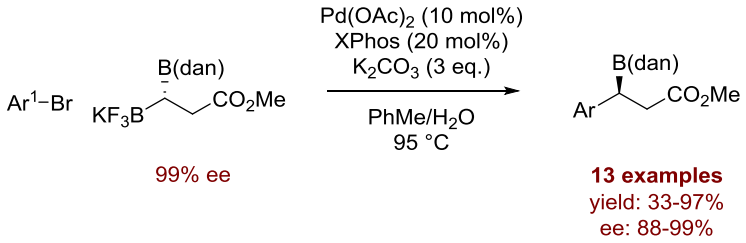
A year later, Molander described a highly stereospecific SM reaction with inversion of stereochemistry.[109] The work employed XPhos as a bulky ligand and worked well with electron-neutral and electron-deficient aryl halides (akin to Crudden's earlier work). In all examples, the stereocentre was β to an amide, and it was concluded that coordination of palladium to the amide was responsible for the inversion



Scheme 23: Selected substrates of Molander's stereoinvertive SM reaction

Suginome and Ohmura were the first to publish examples of stereospecific SM reactions which tolerated the used electron rich aryl halides, again with XPhos being employed as the phosphine ligand.[113] Similarly to Molander, inversion of stereochemistry was observed: again, this was most likely due to coordination of palladium to the amide group present in all starting materials. Interestingly, the addition phenol increased the levels of enantiospecificity, and adding $Zr(OiPr)_4$-*i*PrOH in the reaction, caused stereoretention.

Another stereoinvertive example was presented in 2011 when using diboronyl carboxyesters as reported by Hall *et al*.[114] The diboronyl species consisted of a reacting trifluoroborate and a spectating 1,8-diaminonapthalenyl (dan) unit. XPhos is, again, used to elegantly show selective cross-coupling with the BF_3K group, leaving the B(dan) available for further functionalisation. The application of this functional handle is demonstrated with two examples: firstly, with boron speciation to the BF_3K, followed by a SM reaction; secondly, with boron speciation to the BPin, then carbonyl allylboration reaction to afford the homoallylic alcohol.



Scheme 24: Hall's work on diboronyl cross-coupling

The only example of a stereoinvertive SM in the absence of a coordinating group was published by Biscoe *et al*., last year.[111] To the overall detriment of the process, a costly third generation Buchwald pre-catalyst is used, in contrast to the relatively inexpensive phosphine ligands others have employed. The substrate scope presented was relatively varied, and the levels of enantiospecificity (es) were generally high.

1.6 Hydrogenation Reactions

1.6.1 Hydrogenation Reactions with Hydrogen Gas

A hydrogenation reaction involves the treatment of a compound or element with molecular hydrogen (H_2), normally in the presence of a transition-metal catalyst.

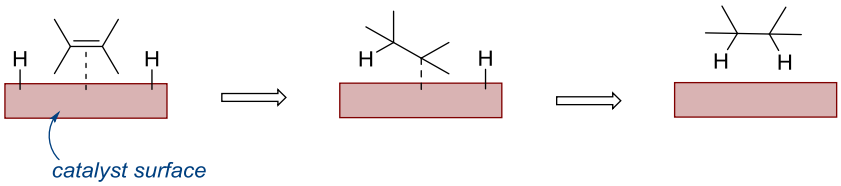


Figure 24: Simplified mechanism of catalytic hydrogenation of alkenes

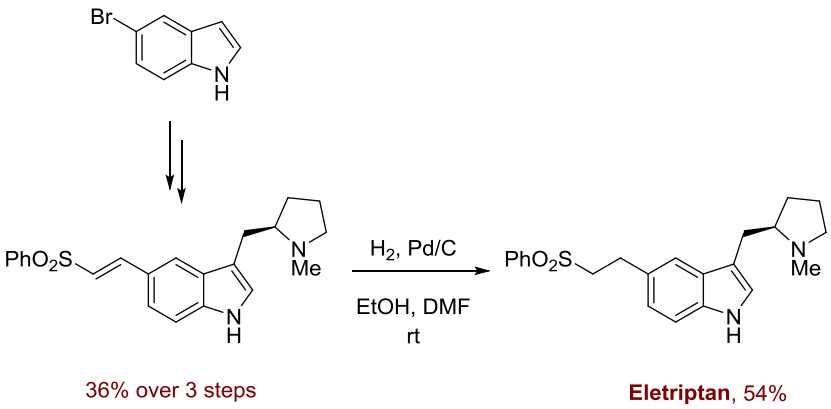
The first reported heterogenous catalytic hydrogenation was nearly 200 years ago, when platinum was used to catalyse the addition of hydrogen to oxygen in Döbereiner's lamp.[115] In 1912, Sabatier won the Nobel Prize in Chemistry for the development of the Sabatier process; work which was inspired by James Boyce's efforts in manufacturing soap products.[116]

In the past century, heterogeneous catalytic hydrogenation reactions have been vastly developed and are used widely in a range of industries. Within the food industry, the largest application of hydrogenation is in the production of vegetable oils. Polyunsaturated fatty acids are partially reduced and the products are used in foodstuff, e.g. margarine. In the petroleum industry, hydrogenation is employed to reduce alkenes and aromatics to alkanes and cycloalkanes (paraffin and naphthene, respectively).

Catalytic hydrogenation is utilised extensively within the pharmaceutical industry. It is the most common technique for the reduction of double-bonds and is also employed for a host of other reductive reactions, including Cbz and benzyl cleavage and nitro/nitrile reductions. From a practical perspective, the procedure is straightforward, and purification is usually facile. Many pharmaceutical companies have abandoned the use of balloons of hydrogen gas, and adopted other techniques for hydrogenations, such as the H-Cube, or hydrogen bombs.

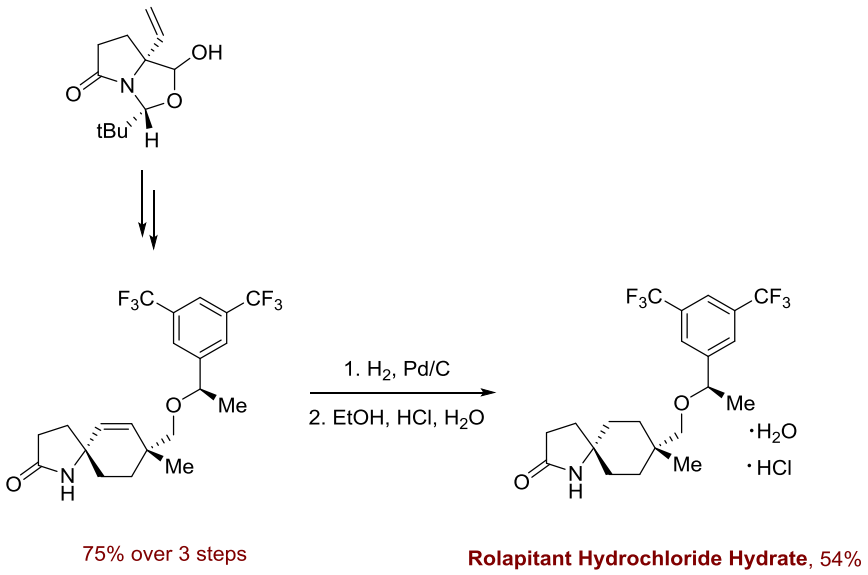
A host of metals can catalyse hydrogenation reactions, including (but not limited to) rhodium,[117] ruthenium,[118] iridium,[119] nickel[120] and iron.[121] For standard alkene reductions, however, the most commonly employed catalyst is palladium on carbon (Pd/C). A carbon support is used to increase the surface area of the catalyst and thereby increase its activity. From Figure 24, it is apparent that the reaction is dependent on the area of surface available for hydrogen and substrate to adsorb, so efforts are made to maximise this. Often, the reaction is performed in specialised glassware which aids to increase surface area.

Hydrogenation reactions with Pd/C are used ubiquitously in a drug discovery setting. Moreover, these reactions are favoured on a process scale because of their simple setup and purification. Eletriptan, a triptan used to treat migraines, and one of the bestselling 5-membered heterocycle containing drugs, employs a Pd/C catalysed hydrogenation in the final step of its synthesis.[122]



Scheme 25: Synthesis of Eletriptan, highlighting the hydrogenation step

In 2015, Rolapitant hydrochloride hydrate (Varubi) was FDA approved for the treatment of chemotherapy induced nausea and vomiting. Again, the final step of this process is a Pd/C catalysed hydrogenation of a cyclic alkene. In Tesaro's synthesis, additional activated carbon is used (presumably to further increase surface area) to furnish the drug in excellent yields.[123]



Scheme 26: Synthesis of Rolapitant hydrochloride hydrate, highlighting the hydrogenation step

1.6.2 Transfer Hydrogenation

Transfer hydrogenation refers to a reaction in which the hydrogen added to a molecule comes from a non-H_2 source. It is often a preferred alternative to reactions using hydrogen gas as it does not involve potentially hazardous flammable gases, and the hydrogen donors are generally readily available and inexpensive. Knoevenagel first demonstrated the concept in the early 1900s when he showed that palladium black could promote the disproportionation of dimethyl 1,4-dihydroterephthalate to dimethyl terephthalate and *cis*-hexahydroterephthalate.[124] Hydrogen transfer reactions were subsequently categorised by Braude and Linstead as follows:[125] 1) hydrogenation disproportionation, where transfer occurs between identical donor and acceptor units; 2) hydrogen migration, which takes place within one molecule; and 3) transfer hydrogenation dehydrogenation, occurring between different donor and acceptor molecules. The 3rd class, which is now commonly referred to as transfer hydrogenation, is the most widely explored.

The ability of a molecule to serve as a hydrogen donor lies in its oxidation potential and a myriad of compounds with low oxidation potentials are suitable. Alcohols, hydrazines, cyclic olefins and hydroaromatics have operated as donors in transfer hydrogenation reactions, but formic acid and its salts are the most prevalent choice. Its preponderance is due to the fact that a stable molecule of CO_2 is released, making the hydrogen donation irreversible. Similarly, there are a raft of homo- and heterogeneous metal-catalysts which can facilitate transfer

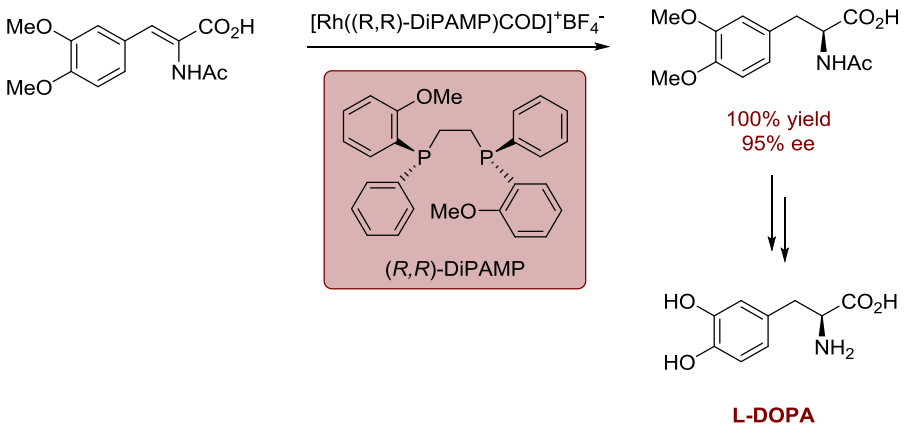
hydrogen reactions. For formic acid, heterogeneous catalysts are usually employed and, as discussed above, Pd/C is the most prevalent.

Mechanistically, palladium-catalysed alkene transfer hydrogenation begins with the chemisorption of formate salts with the metal surface. Succeeding decomposition yields CO_2 and H ions, which are adsorbed to the palladium and subsequently transferred to the substrate.

Like its hydrogen gas counterpart, transfer hydrogenation reactions with ammonium formate are capable of far more than just alkene reductions. Some of the possible transformations are hydrazones and azines to hydrazines; azides and nitros to amines; nitriles to amines or methyl groups and dehalogenation of aryl halides. Additionally, an assortment of functional groups can be cleaved, including Cbz and benzyl.[126]

1.6.3 Asymmetric Hydrogenation with Hydrogen Gas

The first breakthrough with asymmetric hydrogenation came in the late 1960s when William Knowles (2001 Nobel Prize in Chemistry winner for his work on asymmetric hydrogenation) used a rhodium catalyst bearing a chiral phosphine to achieve optically active compounds from prochiral alkenes.[127] The levels of stereoselectivity were modest, but within the next decade, vast improvements were made. In fact, by the 1983, Knowles' work had its first industrial application in the synthesis of Parkinson's drug, L-DOPA.[128]



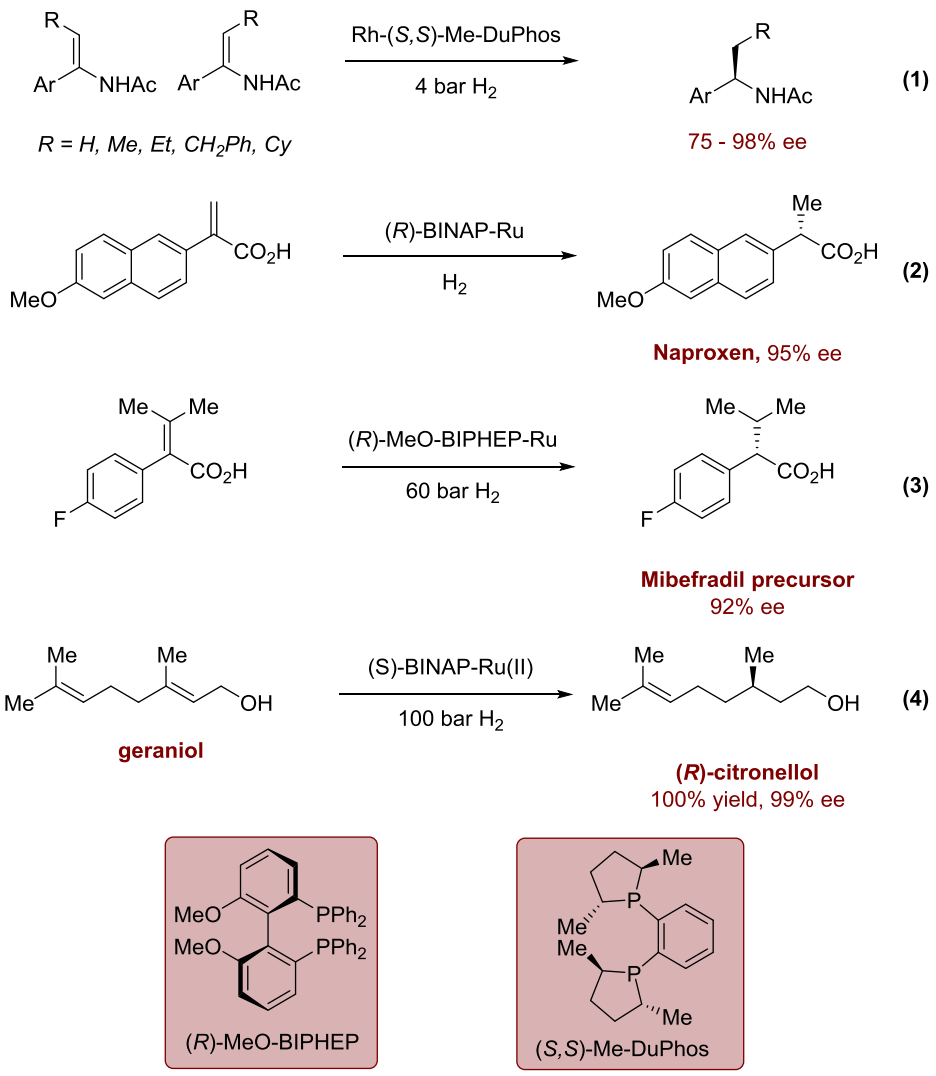
Scheme 28: Knowle's synthesis of L-DOPA

The next significant series of discoveries within the field came from the laboratory of Noyori (the other recipient of the 2001 Nobel Prize in Chemistry), in the late 1980s.[129–131] Chiral complexes based on Ru(II)-BINAP complexes were utilised in the asymmetric hydrogenation of olefins and ketones with exceptional levels of enantioselectivity. This unsurprisingly had a

substantial impact on the chemical industry, and initiated a widescale investigation into furthering the asymmetric hydrogenation reaction.

Asymmetric hydrogenation reactions are not limited to rhodium and ruthenium, and in the last decade iridium has been utilised extensively. Palladium,[132] titanium[133] and platinum[134] have also been shown to be capable catalysts for the reaction.

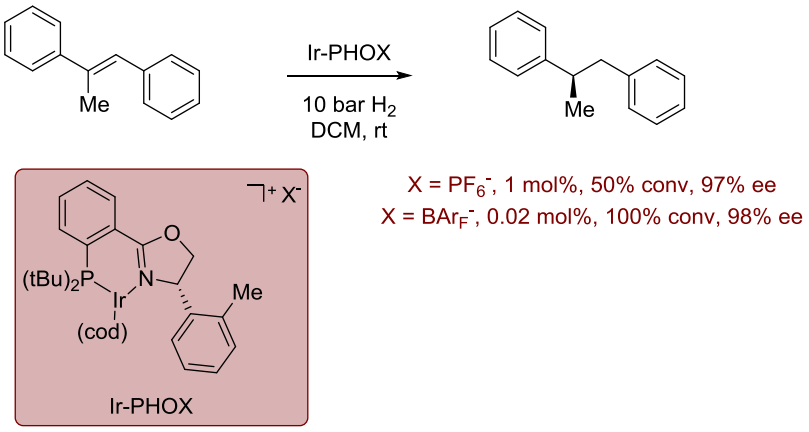
A common trend with asymmetric hydrogenations is the requirement of a proximal functional group which can direct the reaction. Often, ligands and catalysts are designed with a neighbouring group in mind and, because of this, catalyst systems are generally specific for a concise substrate set. As exemplified with the synthesis of L-DOPA, dehydroamino acids make excellent substrates for asymmetric hydrogenation reactions. A range of mono- and di-phosphorus chiral ligands with extreme structural diversity have been developed for this class of substrates. Similarly, enamides, unsaturated carboxylic acids/esters and alkenes with pendant alcohols or amines have all been reduced asymmetrically using a range of metals and ligands. Non-traditional directing groups have also been utilised within this reaction manifold, particularly within iridium catalysis, including fluorine and silicon containing compounds.[135]



Scheme 29: Examples of directed asymmetric hydrogenations: 1) Burk's general conditions to reduce β- substituted enamides;[136] 2) Noyori's synthesis of Naproxen using (R)-BINAP;[137] 3) Hydrogenation step in Roche's synthesis towards Mibefradil;[138] 4) Noyori's selective allylic alcohol hydrogenation to afford (*R*)-citronellol[139]

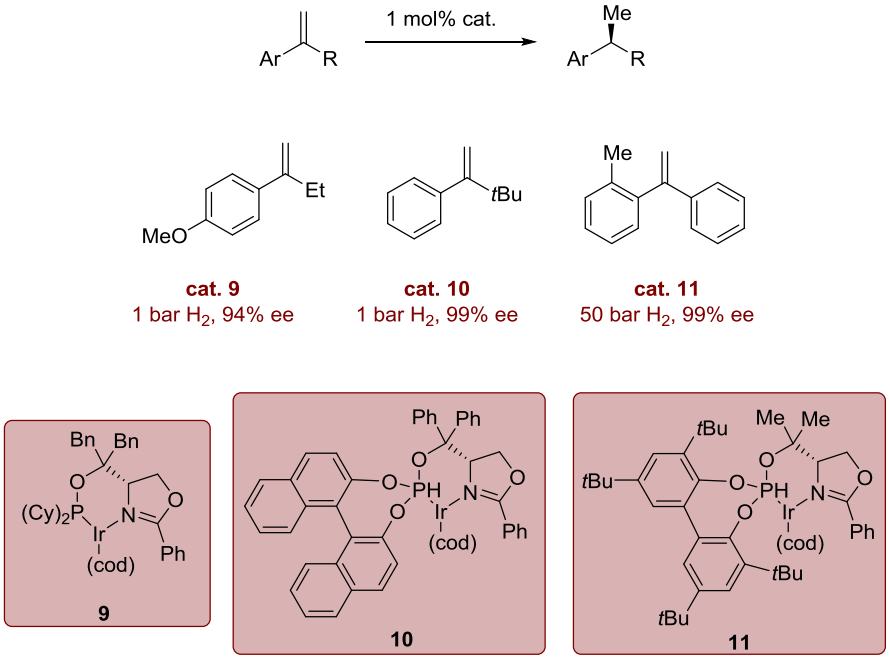
Despite the excellent progress made in the field of asymmetric hydrogenation, the scope of 'unactivated' alkenes is somewhat limited. Whilst high levels of enantioselectivity have been reported for titanium and zirconium metallocene catalysts, their difficult syntheses and troublesome handling detracts from their achievements.[140]

Iridium based catalysts have had most success with unactivated alkenes. Pfaltz *et al.* showed that a Ir-PHOX catalyst (Scheme 30) was effective for a series of unfunctionalized tri-substituted alkenes.[141] The counterion was found to be key in this reaction: BArF complexed well with iridium and inhibited the deactiviation of catalyst, which was observed when PF_6 was used.



Scheme 30: Pfaltz's asymmetric hydrogenation of unfunctionalized tri-substituted alkenes

Several years later, the same group reported a catalyst system capable of reducing disubstituted terminal alkenes asymmetrically.[142] Despite the high reactivity of these alkenes, achieving reasonable levels of enantioselectivity has proven extremely difficult. More recently, a combined combinatorial investigation by Dieguez, Andersson and Borner discovered catalyst systems **10** and **11**.[143] **10** was found to perform remarkably for alkyl-aryl terminal alkenes, where **11** could successfully distinguish between two different aryl groups. To this date, no examples of terminal alkenes which do not contain aryl groups have been reported.



Scheme 31: Examples of asymmetric hydrogenation of disubstituted terminal alkenes

Mechanistically, opinion is divided between two different theories as to how homogeneous catalysts operate: the unsaturated mechanism and the dihydride mechanism. The former

involves the formation of catalyst-substrate complex (**12**) before the hydrogen activation step (Figure 25). Since the first isolation of a catalyst-substrate complex by Brown and Chaloner,[144] numerous others have been reported, and it is the stability of these which has led to the unsaturated mechanism becoming more widely accepted.[145,146] The latter mechanism regards the transient formation of a dihydride rhodium complex (**13**) which are often solvated. Compared to catalyst-substrate complexes, detection of solvate dihydrides has remained elusive.[147]

The difficulties in distinguishing between the two mechanisms is trivialised by the fact that both pathways converge at a common intermediate (**14**) before any stereo-selection occurs.

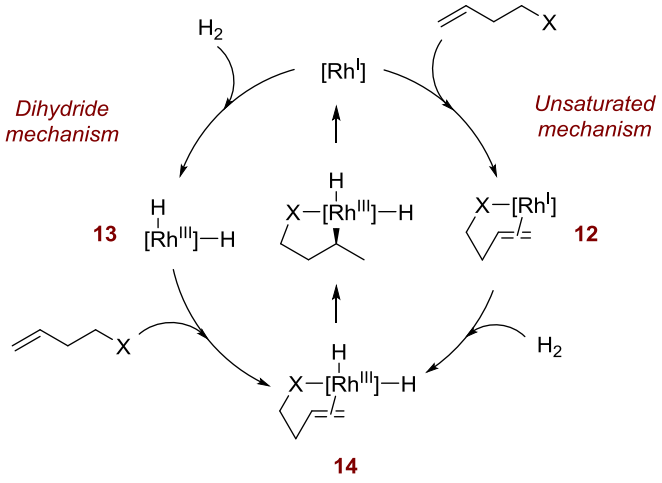
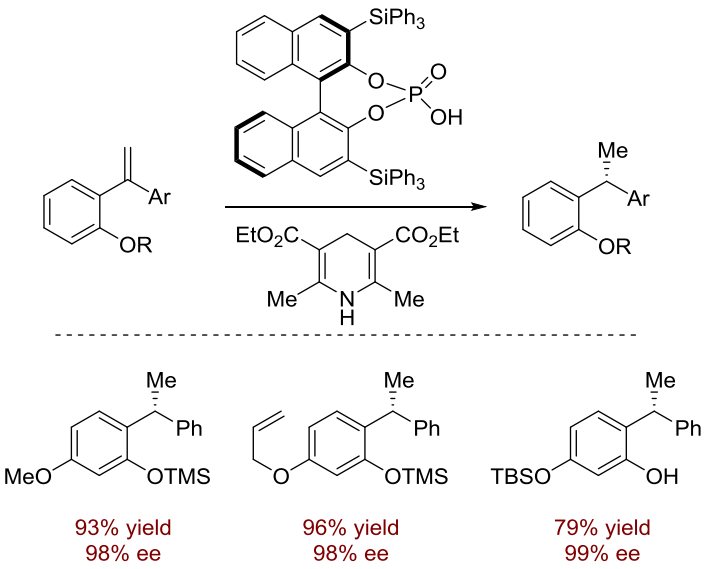


Figure 25: Both proposed mechanistic pathways of rhodium-catalysed asymmetric hydrogenation

1.6.4 Asymmetric Transfer Hydrogenation

Over the past 2 decades, asymmetric transfer hydrogenation (ATH) reactions have also made significant progress. A palette of transition metals has been exemplified as suitable catalysts, in combination with nitrogen, oxygen, phosphorus, carbon and sulfur-based ligands (e.g. as metal *N*-heterocyclic carbenes (NHC), multidentate metal complexes etc.). The requirements for ATH reactions are related to the hydrogen gas variant in that a neighbouring directing group is often required. Iridium, ruthenium and rhodium are the most commonly employed metals,[148] however, recent research has seen other metals perform efficiently (e.g. Co,[149] Ni,[150] Pd[151]), as well as phosphoric acid catalysts.[152] The hydrogen source can vary, but formic acid salts, silanes or isopropanol are the prevailing reagents. An example of the use of Hantzsch ester in an ATH is shown below in Scheme 32.

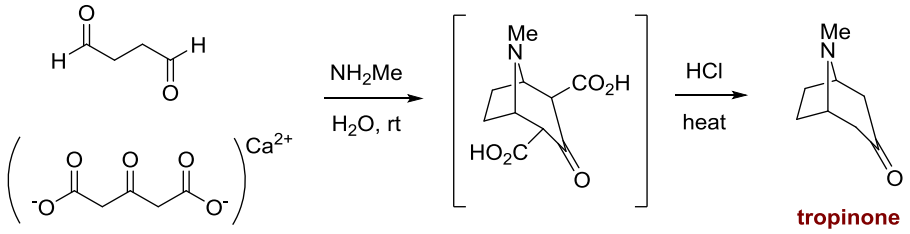


Scheme 32: Selected examples of ATH using a phosphoric acid catalyst as Hantzsch ester as hydrogen source

1.7 One-Pot Syntheses

At almost every stage of chemistry in all industries, efficiency and sustainability are central issues which one must consider. An approach which can improve the effectiveness of a chemical route is to combine two or more reactions in a single vessel; a method which is commonly labelled 'one-pot'. Not only are purification and work-up procedures minimised, but chemical waste is abated, time is saved, and the cleaning process is simplified.

The one-pot technique is certainly not new: indeed, Robinson's landmark tropinone synthesis was published a century ago.[153]



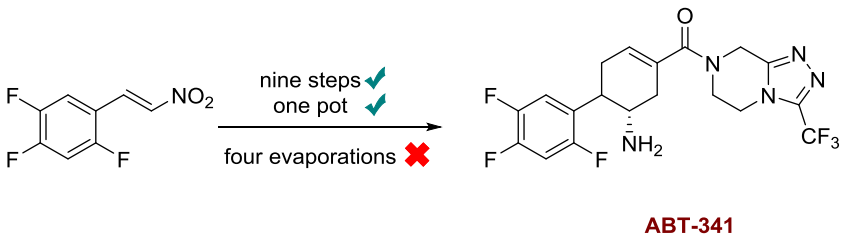
Scheme 33: Robinson's one-pot synthesis of tropinone

Over the past 100 years there have been countless examples of one-pot syntheses, but since the turn of the century the field has seen a surge of interest as the chemical industry has felt an increased pressure to perform reactions within the principles of 'green chemistry'.[154] A debate which has arisen is one regarding terminology. In a recent review entitled *Cascade Reactions*

in Total Synthesis, Nicolaou suggested that the terms 'one-pot-', 'cascade-' 'domino-' and 'tandem-reactions' are interchangeable.[155] Others have proposed that each term has a different definition and the classification of reaction should change depending on whether reagents have to be added sequentially and if the second reaction occurs as a result of the first.[156,157]

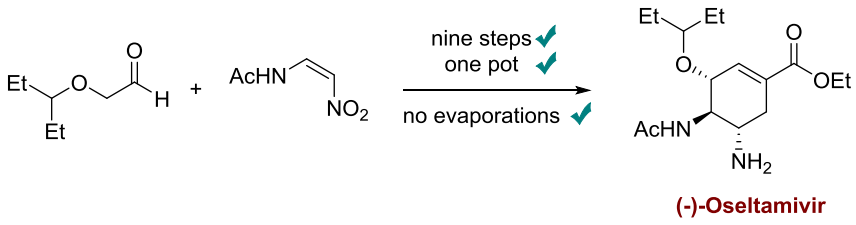
Regardless of definition, one-pot processes generally increase the overall efficiency of a reaction. There are four main metrics associated with this: atom economy, proposed by Trost;[158] step economy, proposed by Wender;[159] redox economy, proposed by Baran;[160] and pot economy. One-pot procedures have the potential to maximise all of these metrics, but will always improve the overall pot-economy.

Recent publications have provided impressive examples of extremely pot-economical syntheses. In 2011, Hayashi and co-workers demonstrated a one-pot, nine-step synthesis of ABT-341, a DPP4 (dipeptidyl peptidase IV) inhibitor drug candidate.[161] The sequence involved an enantioselective Michael addition as a key step, but the route required several solvent changes. This detracts from the efficiency of the process, and many would therefore not consider this route truly one-pot.



Scheme 34: One-pot synthesis of ABT-341 by Hayashi *et al*

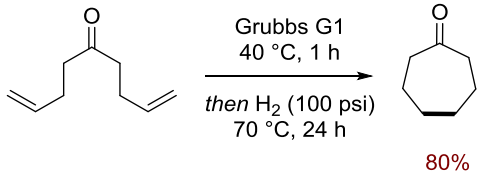
Two years later, however, the same group published another one-pot, nine-step synthesis, this time of (-)-oseltamivir, an antiviral medication used to treat influenza A and B.[162] This route also included an enantioselective Michael addition but did not require any solvent changes or evaporations, allowing it to be truly classed as one-pot.



Scheme 35: One-pot synthesis of (-)-oseltamivir by Hayashi *et al*

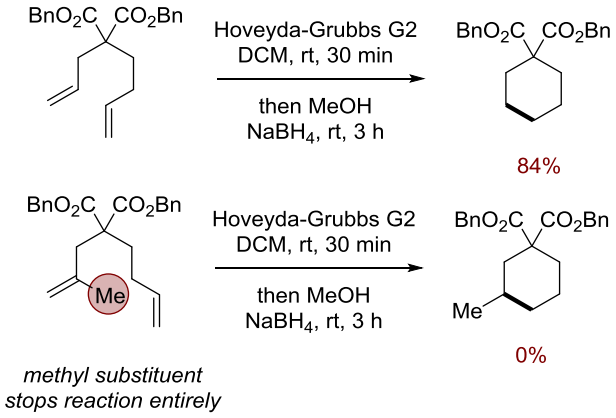
1.7.1 One-Pot Syntheses Incorporating a Hydrogenation Reaction

The single-pot transformations with most relevance to this thesis are reactions involving a hydrogenation. One reaction which has been utilised in several one-pot-hydrogenation protocols is ring closing metathesis (RCM), due to capability of Grubbs catalysts to facilitate hydrogenation reactions. The first example of this was performed by Grubbs' own group in 2011 (Scheme 36),[163] however the methodology was impractical on many levels. A glovebox was required for the reaction setup, high temperatures were used in the hydrogenation step and a pressurised hydrogen atmosphere was required for trisubstituted alkenes (up to 1000 psi). Additionally, the scope was limited in terms of functionality, indicating little reaction tolerance.



Scheme 36: Example of Grubbs' one-pot RCM-hydrogenation

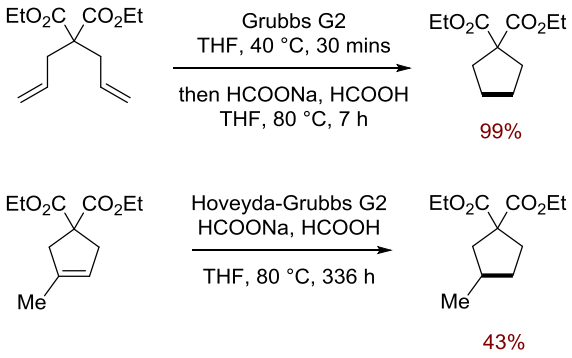
In 2014, Peese *et al.* published what they described as a tandem RCM/transfer hydrogenation.[164] This study used sodium borohydride ($NaBH_4$) as the hydrogen donor, and a Hoveyda/Grubbs catalyst. The reaction used very mild conditions with short reaction times, however, the substrate scope again was poor, and the reaction completely failed with trisubstituted alkenes (Scheme 37).



Scheme 37: Examples of Peese's one-pot RCM-transfer hydrogenation

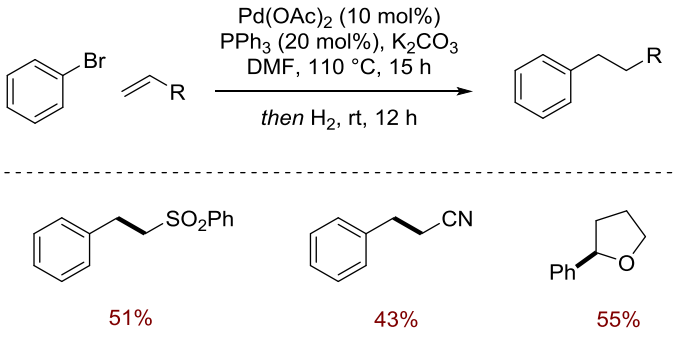
A few months later, this work was further developed by Grela's group.[165] They presented a similar method which utilised formic acid and sodium formate as hydrogen donors. Higher

temperatures were necessary for each step (40 °C and 80 °C), and only 4 examples were given for the one-pot procedure. The transfer hydrogenation step was performed on a range of isolated disubstituted olefins and, when the reaction time was increased to 2 weeks, a single example of reduction of a trisubstituted olefin was achieved. A 2-week-long reaction is not a practical approach, and represents no real advantage over current hydrogenation techniques.



Scheme 38: Examples of Grela's one-pot RCM-transfer hydrogenation

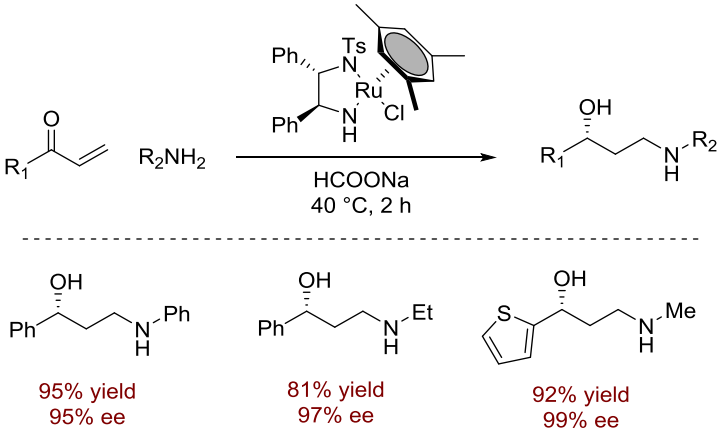
More closely related to the current study is the work of Evans' group with their work on a one-pot Heck-hydrogenation protocol.[166] A palladium catalyst was utilised to enable the coupling of an aryl bromide and monosubstituted alkenes with a subsequent hydrogenation. Large catalyst and ligand loadings were required (10 and 20 mol% respectively), along with high temperatures and relatively long reaction times. The functional group tolerance was acceptable, with amines, esters, sulfones and ethers present in successful substrates. The applicability of the reaction would be greatly increased with the application of acyclic di- or trisubstituted alkenes, however, regioselectivity issues may arise.



Scheme 39: Selected examples of Evans' one-pot Heck-hydrogenation

The most recent example of a one-pot multi-step hydrogenation reaction is Liu's 2017 publication reporting a Michael addition-asymmetric transfer hydrogenation.[167] Using a

bespoke, chiral ruthenium catalyst, they elegantly synthesise a range of chiral γ-amino alcohols, in excellent yields with almost complete stereoselectivity.



Scheme 40: Selected examples of Liu's one-pot Michael addition-asymmetric transfer hydrogenation

2. Project Aims

As previously discussed, the level of saturation in candidate molecules is an important consideration in drug discovery. In light of findings regarding the positive effects of compounds with a high Fsp^3, there has been a considerable volume of research into methods to synthesise highly saturated chemical structures which are increasingly prevalent in modern medicinal chemistry. The motif on which this thesis is focussed is represented by **15** (Figure 26) and, in recent years, work emerging from medicinal chemistry laboratories has furnished a plethora of biologically active compounds which embody this general structure. Specific examples of compounds, which span a range of therapy areas, include adrenergic antagonists (**16**),[168] BACE (Beta-secretase) inhibitors (**18**),[169] and dopaminergic antagonists (**17**).[170]

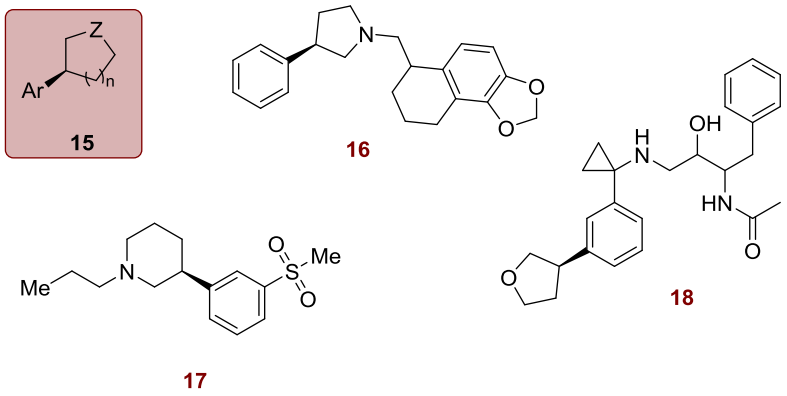
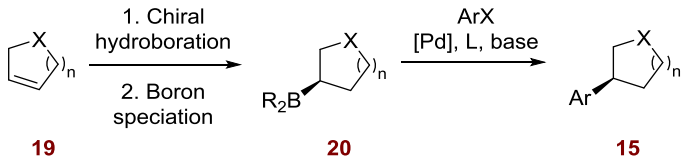


Figure 26: Examples of C-aryl linked saturated heterocyclic systems of biological relevance.

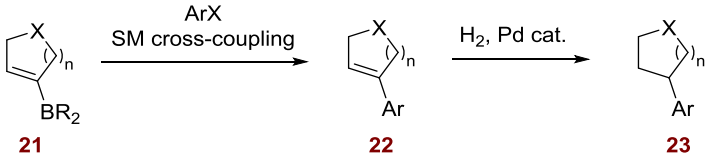
The key disconnection of interest to the research described herein is sp^2-sp^3 carbon-carbon bond indicated on **15**. Retrosynthetic analysis of this motif resulted in proposal of several different routes. The first approach involves the development of a modular synthesis towards an enantioenriched boron species (**20**), on which sp^2-sp^3 coupling methodology could be performed.



Scheme 41: Proposed overview of first synthetic approach

Using this approach, chirality could be induced in the hydroboration step, followed by a stereoretentive or stereoinvertive sp^2-sp^3 cross-coupling reaction, building on existing precedent for such transformations, to enable synthesis of **15**.

The second approach is an sp^2-sp^2 SM cross-coupling, followed by a reduction of the resulting styrenyl bond, in a one-pot fashion. This method would take advantage of the large range of commercially available vinyl boron species, as well as the vast functional group tolerance of the SM reaction. Using this method, however, inducing asymmetry is less clear, and could potentially be possible through an asymmetric hydrogenation. Having said that, examples of enantioselective hydrogenation reactions of unfunctionalised alkenes without the presence of a directing group are scarce, and often require highly pressurised systems.



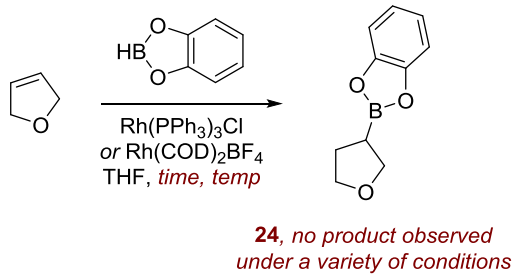
Scheme 42: Proposed overview of second synthetic approach

With a drug discovery application which is at the forefront of motivation behind this research, it is vital that the developed methodology: 1) has a high functional group tolerance, 2) is operationally simple, and 3) is ameanable to array chemistry, enabling rapid analogue synthesis. These considerations were used to influence the synthetic design at the heart of the current study.

3. Results and Discussion

3.1 Racemic Hydroboration of Heterocycle Alkenes

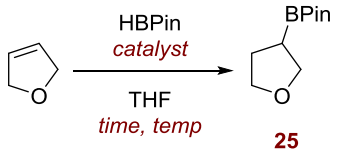
The first task in the project was to develop an achiral route towards the desired boron species, which began with the hydroboration of a saturated heterocyclic olefin shown below. Given the lack of generally applicable sp^2-sp^3 coupling protocols, it was envisaged that access in the first instance to racemic material would be valuable in optimising the cross-coupling before consideration of the stereochemical aspects of the process. Catecholborane was initially employed as the boron species, due to its wide application within hydroboration processes. The reaction was attempted under a variety of conditions, both catalysed and non-catalysed, however, limited levels of success were observed. Sp^3 boronic esters are inherently unstable, and catechol boronic esters in particular suffer from a fundamental instability, so it is probable that any product was degraded upon being applied to acidic silica chromatography. The use of alumina column chromatography and reverse phase chromatography did not alter the outcome, however.



Scheme 43: Attempted hydroboration using catecholborane (full range of conditions in Experimental section)

The hydroborating agent was changed to pinacolborane (due to its increased stability)[71] and applied to a similar range of conditions as before. In this case, Wilkinson's catalyst was the most competent additive, and increasing the temperature or time did not have a significant effect on the outcome of the reaction. Pleasingly, the desired compound was isolated in 55% yield. This process was effective up to a 10 mmol scale, although at which point the yield decreased to lower than 40%.

Table 1: Optimisation of achiral hydroboration with pinacolborane



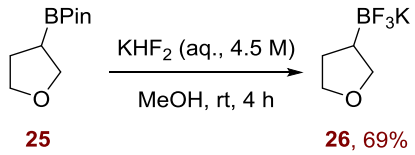
25

Entry	Catalyst	Temperature	Time	Yield (%)
1	-	25	16	0
2	-	40	16	0
3	-	60	16	0
4	$Rh(PPh_3)_3Cl$	25	16	55
5	$Rh(PPh_3)_3Cl$	40	16	56
6	$Rh(PPh_3)_3Cl$	60	16	50
7	$Rh(PPh_3)_3Cl$	25	48	50
8	$Rh(COD)_2BF_4$	25	16	0
9	$Rh(COD)_2BF_4$	40	16	0
10	$Rh(COD)_2BF_4$	60	16	0
11	$Rh(COD)_2Cl_2$	25	16	0
12	$Rh(COD)_2Cl_2$	40	16	0
13	$Rh(COD)_2Cl_2$	60	16	0

With the desired boronic ester successfully synthesised, efforts were focussed on the transformation to the analogous trifluoroborate salt. As discussed above, the synthesis of BF_3K salts from other boron species has been extensively documented and the most regularly used method involves the treatment with an aqueous KHF_2 solution. Initially, THF was used as the solvent, however, due to the limited solubility of water and THF, a significant bilayer was

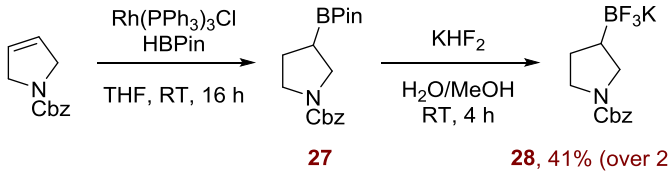
forming which appeared to inhibit the reaction. To rectify this, the solvent was changed to MeOH. This change was beneficial and the desired BF_3K was isolated in a 70% yield. The results of this reaction were not consistent, though, and the yield varied from 20% to 70%. The isolation procedure was found to be key in achieving a good yield and was investigated in detail. The optimised work-up protocol included the following steps:

1. Concentration of the reaction mixture *in vacuo*
2. Extraction of the resultant white solid with 4:1 acetone:MeOH three times
3. Concentration of the extracted solution *in vacuo* to the point at which a precipitate appears in the flask
4. Addition of Et_2O and filtration of the white solid salt



Scheme 44: Transformation of tetrahydrofuran BPin to corresponding BF_3K

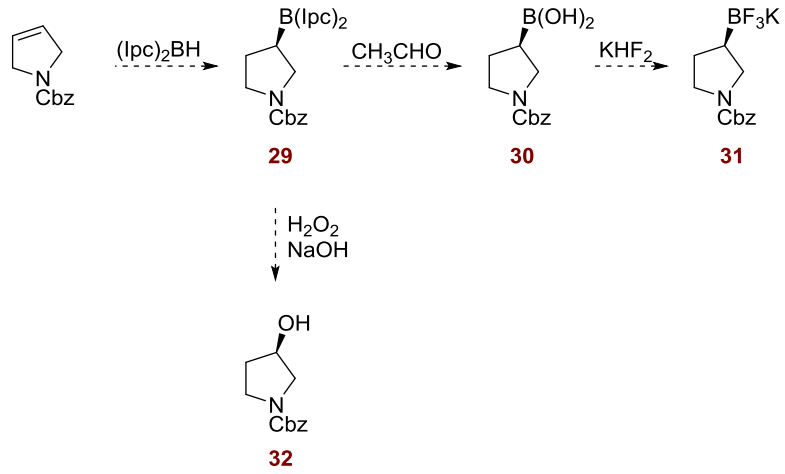
Additionally, the optimised process could be applied successfully to other saturated heterocyclic olefins, including the Cbz-protected pyrrolidine shown below.



Scheme 45: Application of hydroboration and subsequent boron speciation to pyrrolidine scaffold

3.2 Enantioselective Hydroboration of Heterocycle Alkenes

In parallel to the development of racemic BF_3K substrates, approaches to chiral analogues were also investigated, which were more difficult to achieve than had been initially expected. The first two steps in the route outlined below were published by Brown in the 1980s, although reports of the work suffer from various discrepancies in terms of experimental procedures.

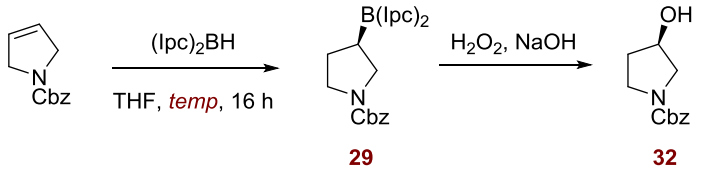


Scheme 46: Proposed route towards enantioenriched BF_3K

Nevertheless, the initial step in the process was to perform an enantioselective hydroboration. Due to thermal and aerobic instability, $(Ipc)_2BH$ must be generated *in situ*. Organoborane **29**, like its boron precursor, is thermally and aerobically unstable. As a result of this, **29** cannot be isolated, and the levels of enantiopurity cannot be determined directly. Instead, **29** was subjected to an oxidative work-up with H_2O_2 and NaOH, yielding the **32**. The mechanism of this reaction is known to occur with full retention of stereochemistry, therefore the ee of the resultant alcohol could be used to confidently determine the ee obtained from the hydroboration step. In general, the oxidation step occurs in quantitative yields, also allowing the yield of the hydroboration to be accurately estimated.

Table 2 shows the levels of ee obtained whilst using $(Ipc)_2BH$, although a lack of consistency is apparent throughout. In general, one would expect the degree of enantioselectivity achieved to increase with decreasing temperature, but this trend was not observed within this dataset. Note that in the investigation in Table 2, yields were not recorded.

Table 2: Hydroboration using $(Ipc)_2BH$ at varying temperatures



Entry	Temperature (^{0}C)	ee (%)[a]
1	25	50, 52, 65, 50
2	0	62, 62, 66, 58
3	-25	50, 60, -20, 20

a) determined by chiral HPLC

Amongst the inconsistencies, Entry 3.3 strangely shows the formation of the opposite enantiomer (ee = -20%). A thorough search of the literature found that $IpcBH_2$ can hydroborate to form one enantiomer, whilst $(Ipc)_2BH$ will form the other.[171] Research by Brown also showed that during the formation of either hydroborating agent, the two are in equilibrium with each other, as illustrated below:

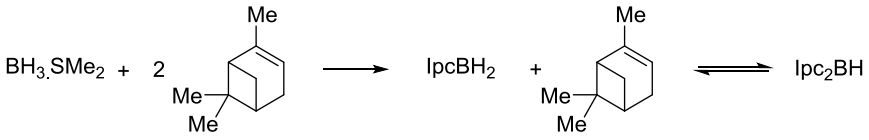
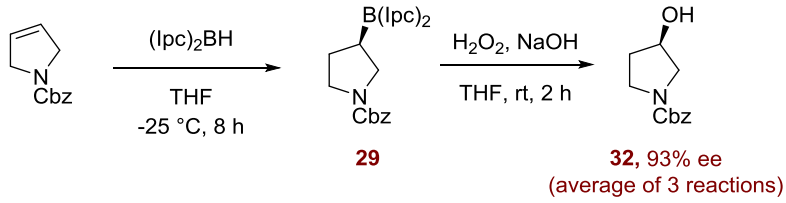


Figure 27: Equilibrium between $(Ipc)_2BH$ and $IpcBH_2$

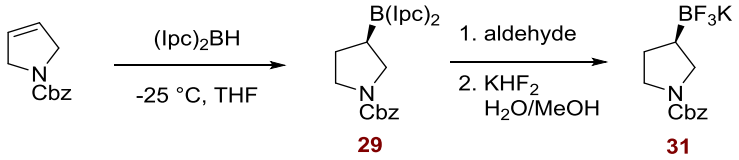
It was reasoned that during the synthesis of $(Ipc)_2BH$, $IpcBH_2$ was also being formed in varying amounts, and it was the ratio between the two alkyl boranes which determined the levels of ee. To address this, the selective synthesis of $(Ipc)_2BH$ was essential, and thus new reaction conditions were examined. The aim was to shift the equilibrium towards Ipc_2BH, and this was achieved by using 2 equivalents of α-pinene and allowing the reaction mixture to age undisturbed at 0 °C for 3 days. Pleasingly, the levels of enantioinduction increased significantly, and remained reasonably constant (within 4%).



Scheme 47: Increased consistency with hydroboration/oxidation

Subsequently, the transformation of organoborane **29** to boronic acid/ester **30** was explored. Treatment of **29** with various aldehydes has been shown to afford the corresponding boronic ester.[172] When this was attempted with acetaldehyde, no reaction was observed. The reaction was repeated but carried directly through to the BF_3K salt - this yielded a disappointing 7% over two steps, prompting an investigation into the choice of aldehyde. Benzaldehyde, pentafluorobenzaldehyde and chloral hydrate were all used in the reaction. Chloral hydrate appeared to be most effective by TLC and ^{11}B NMR but when carried through to the next step, no product could be isolated. When benzaldehyde and pentafluorobenzaldehyde were used, the yield of BF_3K increased, but this was particularly variable.

Table 3: Investigation into the effect of aldehyde towards the formation of BF_3K salt 31

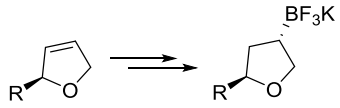


Entry	Aldehyde	Yield of 31 (%)
1	Acetaldehyde	7
2	Chloral hydrate	0
3	Benzaldehyde	20 – 32[a,b]
4	Pentafluorobenzaldehyde	21 – 34[a]

a) yield over >3 attempts, b) single result of 45% was achieved

3.3 Synthesis of Chiral Saturated Heterocyclic BF_3K Salts with Ring-Substitution

Despite varying yields at this step, a relatively reliable method had been established to synthesise the desired chiral BF_3K salt, so efforts were turned towards the synthesis of more functionalised alkyl boron species. Indeed, a diastereoselective hydroboration approach was explored next. By synthesising a range of saturated heterocyclic olefins with chiral substituents, it was assumed that the facial selectivity of the hydroboration reaction could be influenced through substrate control. Additionally, the elaborated structures fit well with the project's focus on synthesising molecules of biological relevance.

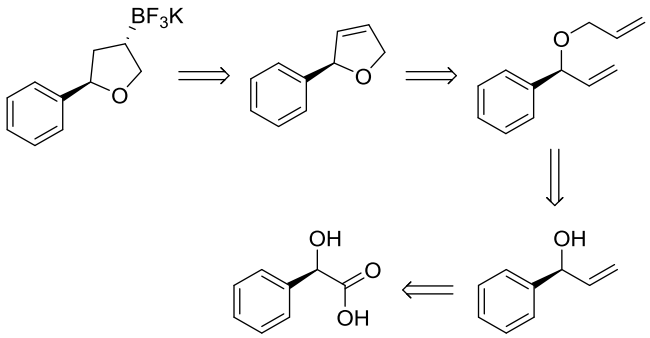


Scheme 48: Example of the proposed diastereoselective hydroboration

The two main classes of heterocycles investigated were oxygen containing (tetrahydrofuran and tetrahydropyran) and nitrogen containing (pyrrolidine and piperidine).

3.3.1 Oxygen Containing Heterocycles

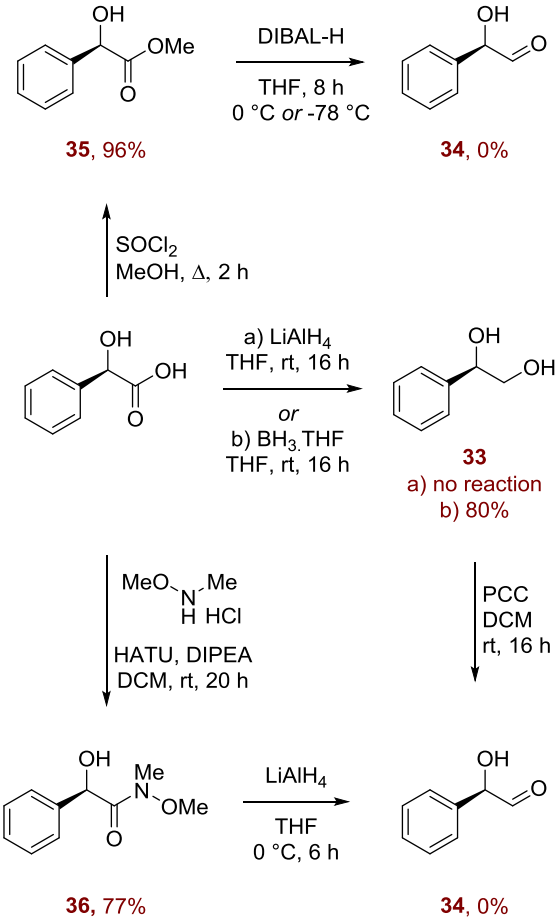
The initial proposal was to begin the synthesis with molecules which had existing chirality, to avoid having to introduce a stereocentre in a potentially challenging step. Mandelic acid was identified as the starting material, as it was available as a single enantiomer at low cost, and other derivatives are commercially accessible, making this an attractive route. The following retrosynthetic analysis was devised:



Scheme 49: Proposed retrosynthetic pathway to enantioenriched BF_3K salt from mandelic acid

The first step of the synthesis was reduction of the acid group to the corresponding aldehyde. The acid was completely reduced to diol **33**, with the intention to re-oxidise it to aldehyde **34**. $LiAlH_4$ was unsuccessful for the initial reduction, however borane-THF produced the alcohol

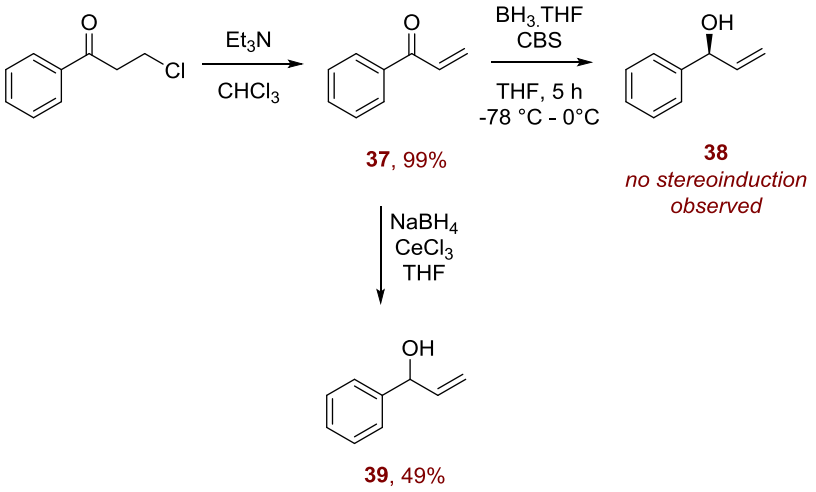
in a good yield. With the diol in hand, a controlled oxidation was attempted. Oxidation with PCC allowed aldehyde **34** to be observed by NMR; however, upon a work-up (which involved filtration through silica) the aldehyde appeared to degrade. As an alternative approach, mandelic acid was esterified *via* the corresponding acid chloride and a reduction using DIBAL-*H* was attempted, although over-reduction to the alcohol was the major product of this reaction. Similarly, the Weinreb amide of mandelic acid was synthesised and subsequently treated with $LiAlH_4$, however, no consumption of starting material was detected so his approach was abandoned.



Scheme 50: Various attempts at the synthesis of aldehyde 34 from mandelic acid

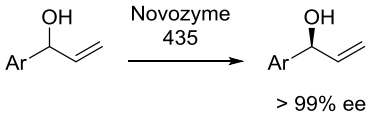
Based on the above, efforts moved towards a different starting material, outlined in Scheme 51. Elimination and reduction of 3-chloropropiophenone resulted in the desired **39**. This alcohol was desired as a single enantiomer, though, so an enantioselective reduction was required. The Corey-Bakshi-Shibata (CBS) reaction is an enantioselective reduction using borane and a chiral oxazaborolidine as a catalyst[173,174] (such reagents were developed in the laboratory of Itsuno, so the reaction is often referred to as the Corey-Itsuno reduction).[175] CBS

reduction conditions proved unsuccessful for the substrate in question, however, despite a range of conditions being tried.



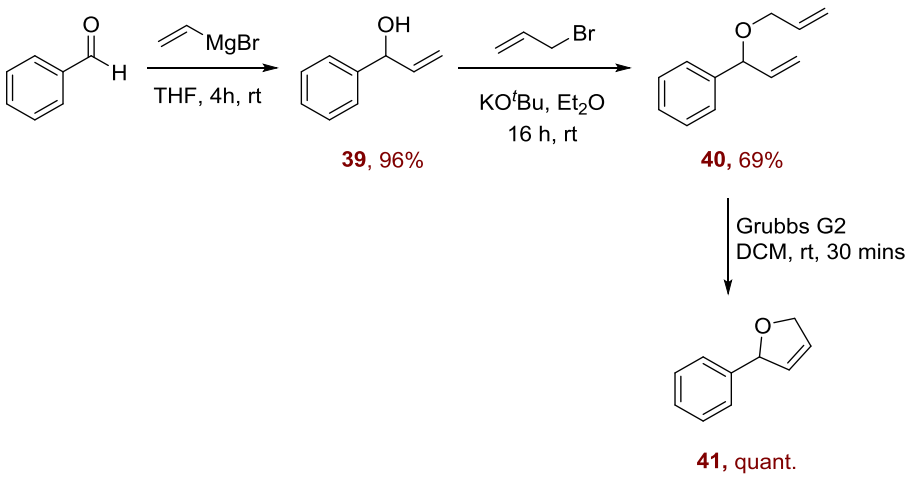
Scheme 51: Synthesis of racemic alcohol 39 and attempted synthesis of chiral alcohol 38

It was the work of Kočovský and co-workers which inspired the a direction towards the synthesis of the target compounds.[176] In 2008, the chiral resolution of benzylic alcohols was demonstrated, with exceptional levels of ee and high yields. Novozyme 435, a lipase recombinant from *Aspergillus oryzae*, was employed to achieve the esterification of a single enantiomer using isopropenyl acetate. Removal of the acetate group allows for both enantiomers of the alcohol to be readily synthesised.



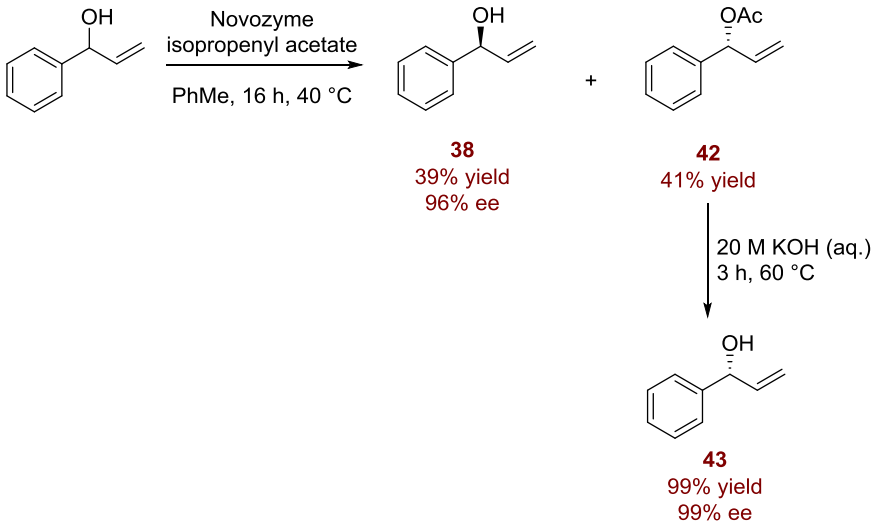
Scheme 52: Chiral resolution of benzylic alcohols by Kočovský e*t al*

Initially, the route to the target dihydrofurans was enabled using a racemic substrate, before the chiral resolution stage was investigated. Grignard addition to benzaldehyde with vinyl magnesium bromide worked excellently on a multi-gram scale. Alkylation of the resulting alcohol worked under a variety of conditions in yields up to 69%, which was followed by an extremely efficient RCM reaction using Grubbs G2 catalyst.



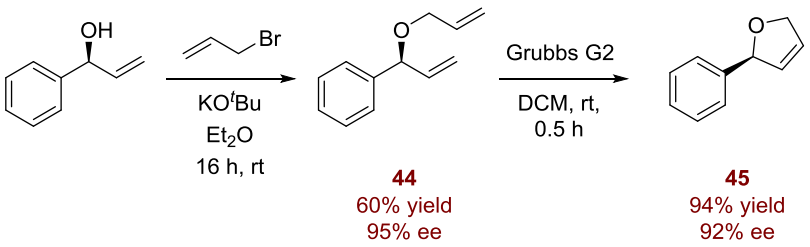
Scheme 53: Racemic synthesis of substituted dihydrofuran 41

Once the synthesis of cyclic olefin **41** had been completed, the chiral resolution was subsequently explored. The use of Novozyme proved successful, affording alcohol **38** and acetate **42** in yields of 39% and 41% respectively. Pleasingly, **38** was found to have an ee of 96%. The concentration of potassium hydroxide (KOH) was found to be critical for acetate cleavage – when a 20 M aqueous solution of KOH was used, the yield was 99% and the ee of the resulting alcohol was also 99%.



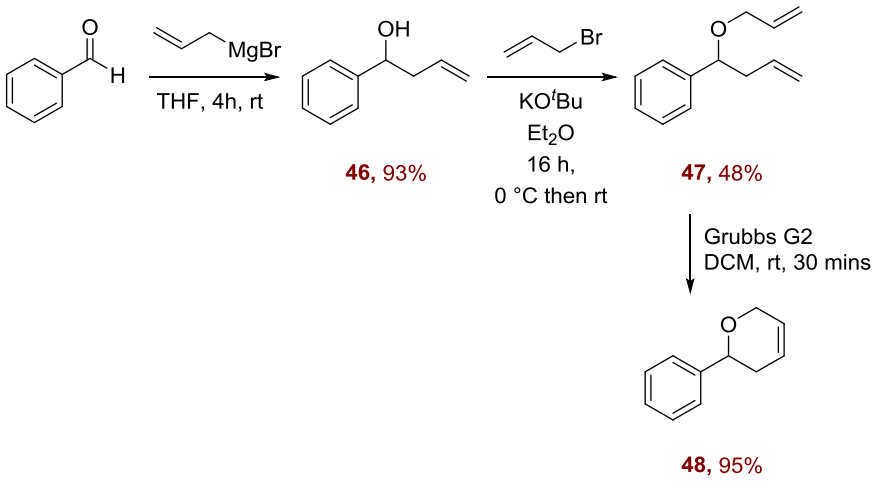
Scheme 54: Chiral resolution of benzylic alcohol

Alkylation of chiral alcohol **38** provided the ether in slightly lower yields than the corresponding racemate. Again, the metathesis step proceeded well with only slightly diminished yields compared to the racemic substrate.



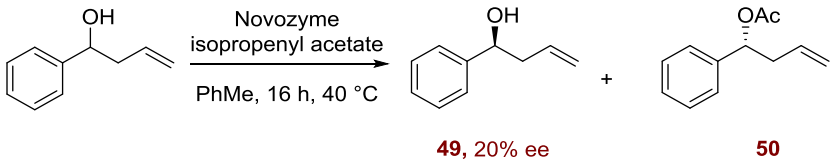
Scheme 55: Synthesis of chiral substituted dihydrofuran 45

The racemic synthesis of a pyran equivalent followed a similar route to **41**, outlined below:



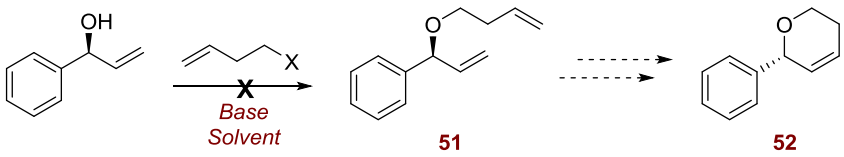
Scheme 56: Synthetic route to substituted dihydropyran derivative 48

Again, following the synthesis of the racemate, resolution of alcohol **46** was attempted. Dissapointingly, the isolated alcohol had an ee of only 20%.



Scheme 57: Unsuccessful chiral resolution of benzylic alcohol

It is likely that Novozyme is only compatible with the vinylic functionality in molecules, due to the specificity of the enzyme. To overcome this problem, the addition of a longer chain to the alcohol was attempted, to ultimately synthesise the regioisomer **52**. Unfortunately, the alkylation was unsuccessful under a range of conditions, so efforts were halted at this point.



Scheme 58: Investigation into the alkylation of 38 to ultimately synthesise dihydropyran core

3.3.2 Nitrogen Containing Heterocycles

In addition to oxygen-containing heterocycles, pyrrole and piperidine cores were also explored. For these examples, chiral auxiliaries were used as the method of chiral induction, an example of second generation asymmetric synthesis. The auxiliary chosen was Ellman's auxiliary, a sulfinamide, which has been utilised to prepare chiral amines with very high levels of diastereoselectivity since its initial disclosure in 1997.[177] Typically, the sulfinamide is reacted with an aldehyde to afford the correpsonding *N*-sulfinyl imine, which is then treated with a nucleophile. The diastereoselectivity is rationalised through a highly rigid 6-membered transition state in which the metal of the nucleophile is chelated oxygen of the sulfinimine.

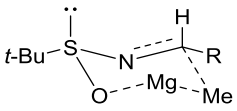
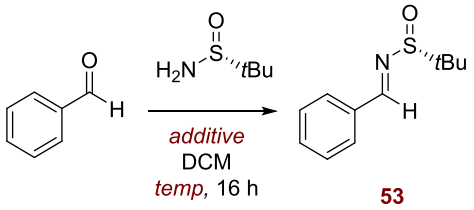


Figure 28: 6-membered transition state for addition to Ellman imine

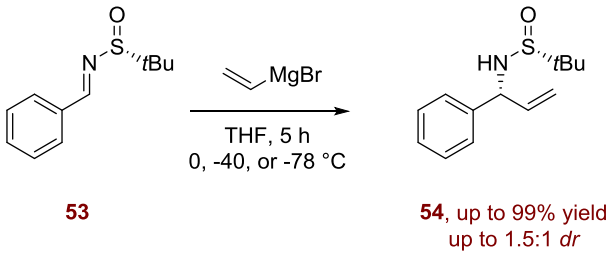
The first step of the route was the formation of *N*-sulfinyl imine **53**, through the reaction with benzaldehyde and *tert*-butyl sulfinamide. There are a range of additives used for the addition of Ellman auxiliaries, though $CuSO_4$ is one of the most common.[178] However, when $CuSO_4$ was added to the reaction, **53** was achieved in only 16% yield. Following this, an alternative method of synthesis was undertaken, this time employing pyrrolidine as a catalyst with a 10 mol% loading, as described recently by Cid *et al.*[179] The reaction was performed in a sealed vessel at 40 °C. The first reaction afforded the desired product with a yield of 93%, however, when the scale was increased, the yield decreased significantly to the point where the reaction was unfeasible. Eventually, caesium carbonate was successfully employed, furnishing **53** in excellent yields which remained consistent with increasing scale.

Table 4: Formation of sulfinimine 53 under a range of conditions



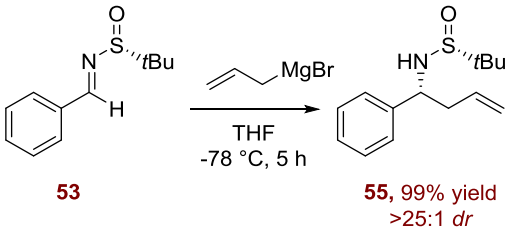
Entry	Additive	Temperature	Scale (mmol)	Yield (%)
1	$CuSO_4$	40 °C	1	0
2	Pyrrolidine	40 °C	1	93
3	Pyrrolidine	40 °C	2	56
4	Pyrrolidine	40 °C	4	10
5	Cs_2CO_3	40 °C	1	93
6	Cs_2CO_3	40 °C	4	91
7	Cs_2CO_3	rt	1	nr

For the synthesis of the pyrroline core, vinyl magnesium bromide was employed as the nucleophile for the subsequent reaction. The reaction was originally attempted at 0 °C, furnishing **54** in an excellent yield. Disappointingly, however, the diastereomeric ratio (dr) was poor. The reaction temperature was lowered to -40 °C and -78 °C, though no increase in the dr was observed. Other vinyl nucleophiles were briefly investigated but the reaction outcome was not improved.



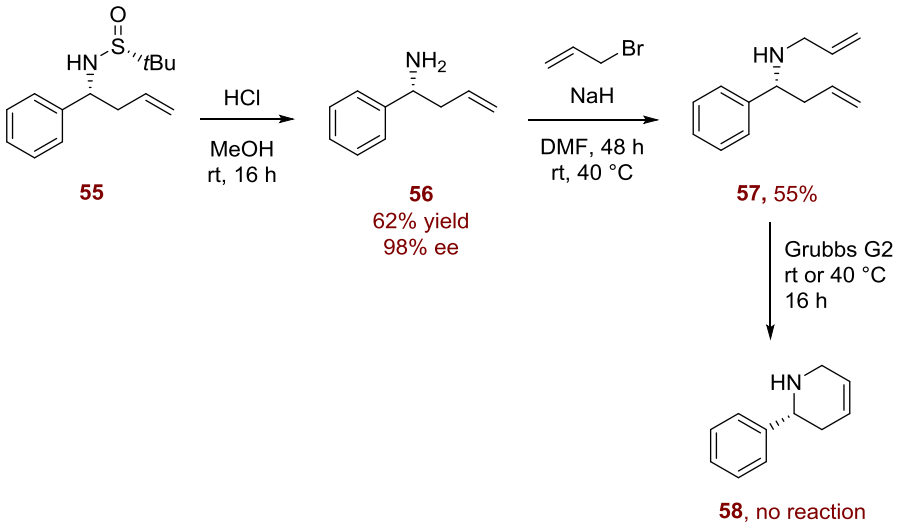
Scheme 59: Addition of vinyl Grignard to sulfinimide 53 at varying temperatures

In an attempt to access the piperidine core, allyl magnesium bromide was employed, with which greater success was achieved. At -78 ^{0}C, the product was synthesised with a 99% yield and >25:1 dr.



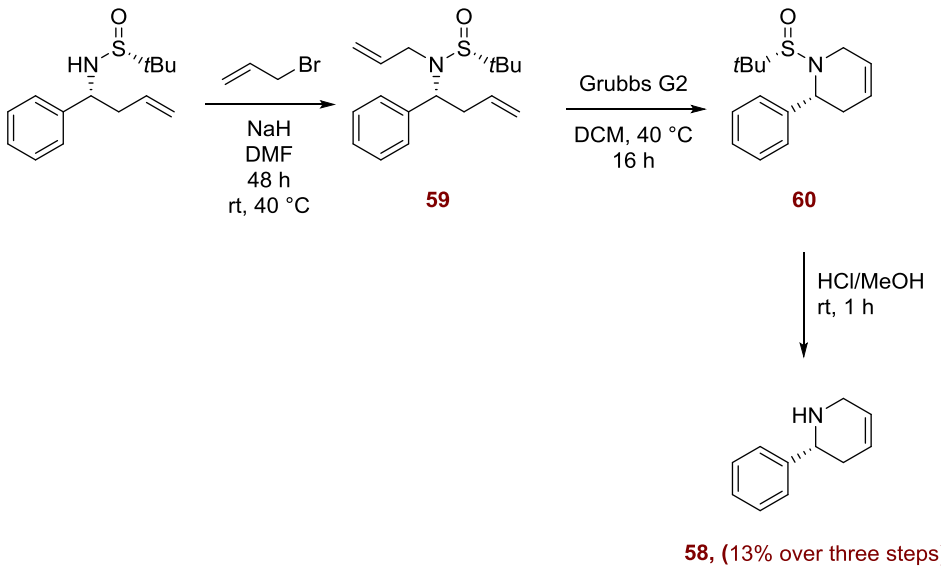
Scheme 60: Successful addition of allyl Grignard to sulfinimide 53

A yield no higher than 62% could be achieved in the deprotection of **55**, despite varying temperature, concentration, and time. Nevertheless, the resulting amine had an ee of 98%. Alkylation of **56** was achieved with NaH and allyl bromide in DMF in acceptable yields. The metathesis of secondary amine **57** was fruitless, however. This result was unsurprising as the presence of basic amines has been shown to diminish the catalytic activity of 1st and 2nd generation Grubbs catalyst. Indeed, a recent publication exhibited that basic amines can displace the ligands, minimising the activity for RCM.[180]



Scheme 61: Deprotection of sulfinamide followed by alkylation and unsuccessful RCM

With this insight, the order of steps was altered to mask the basic centre during the metathesis step. Alkylation was performed directly on sulfinamide, followed by RCM, to provide the ring-closed product in a moderate yield. No catalyst poisoning was observed due to the absence of basic nitrogen atoms in the molecule.

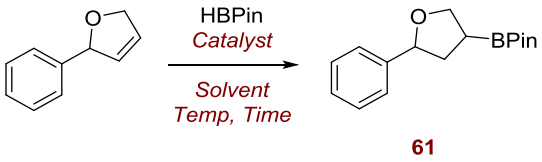


Scheme 62: Alkylation of sulfinamide 55 followed by RCM and subsequent deprotection with HCl

3.3.3 Investigation into Hydroboration of Substituted Olefins

As stated previously, the ultimate objective was to perform a diastereoselective hydroboration on the heterocyclic olefins, followed by a boron speciation to afford the corresponding alkyl BF_3K. Attempts were initially performed on the furan racemate **41**, and a selection of catalysts and conditions were applied to the reaction, as shown below.

Table 5: Investigation into the hydroboration of 41



Entry	Catalyst	Solvent	Temp	Loading	Time	Yield (%)
1	$Rh(PPh_3)Cl$	THF	rt	1	8	0
2	$Rh(PPh_3)Cl$	THF	rt	1	16	0
3	$Rh(PPh_3)Cl$	THF	rt	1	48	0
4	$Rh(PPh_3)Cl$	THF	40	1	16	0

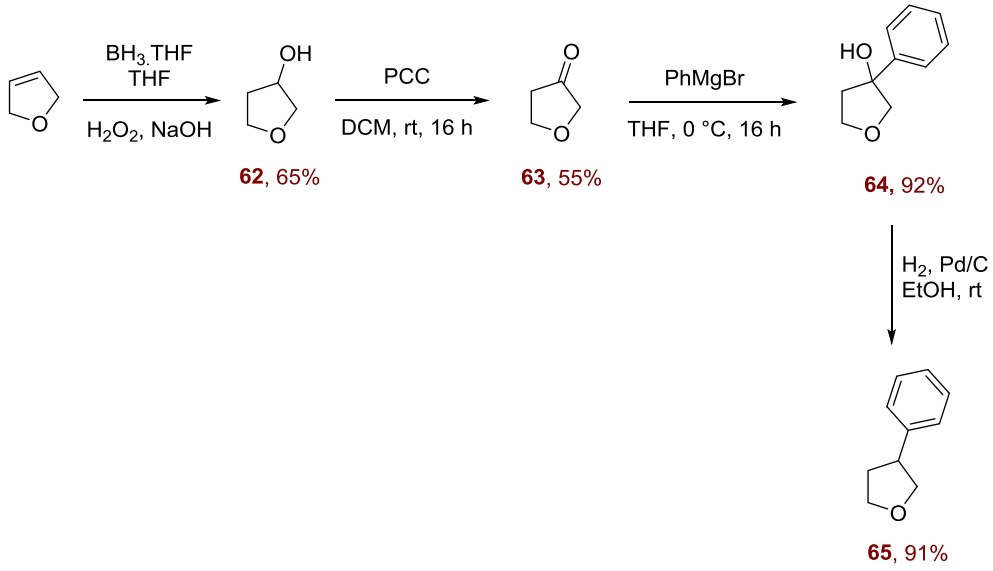
5	$Rh(PPh_3)Cl$	THF	40	1	48	0
6	$Rh(PPh_3)Cl$	THF	60	1	16	0
7	$Rh(PPh_3)Cl$	THF	60	1	48	0
8	$Rh(PPh_3)Cl$	THF	rt	5	16	0
9	$Rh(PPh_3)Cl$	THF	rt	10	16	0
10	$Rh(PPh_3)Cl$	THF	40	5	16	0
11	$Rh(PPh_3)Cl$	THF	40	10	16	0
12	$[Rh(COD)Cl]_2$	THF	rt	1	16	0
13	$[Rh(COD)Cl]_2$	THF	rt	1	48	0
14	$[Rh(COD)Cl]_2$	THF	40	5	16	0
15	CuCl	MeOH/THF	rt	10	16	0
16	CuCl	MeOH/THF	40	10	16	0

Each reaction was monitored by TLC, and in the cases of consumption of starting material, a ^1H NMR was performed to determine the extent of hydroboration. In some cases (namely through the use of Wilkinson's catalyst), olefin protons appeared to have reduced, however, no desired product was isolated, despite attempts at *in situ* oxidation and BF_3K formation. The hydroboration reaction was also attempted on **48**, but this reaction was unsuccessful.

Accordingly, it was concluded that investigations into the hydroboration of the synthesised substituted heterocyclic olefins should be ceased at this point. Despite this, the saturated heterocyclic olefins represent a useful class of molecules which may find application in other areas of chemistry.

3.4 Suzuki-Miyaura Investigation Using Alkyl BF_3K Salts

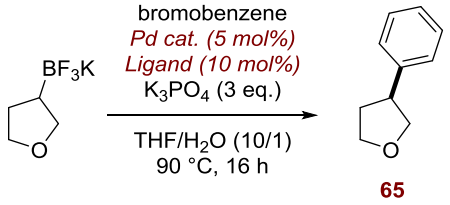
In order to begin screening of the proposed SM reaction initially using a racemic substrate, an HPLC assay was required in order to accurately determine the level of conversion. Accordingly, access to compound **65** was required. The synthesis of the target compound began with a Brown-type hydroboration-oxidation reaction in an acceptable 65% yield. The oxidation of **62** was challenging: typical Swern conditions and the use of Dess-Martin periodinane (DMP) provided no product. The ketone was eventually synthesised using pyridinium chlorochromate (PCC) in a moderate yield. Treatment of ketone **63** with phenylmagnesium bromide provided tertiary alcohol **64** in an excellent yield, followed by a hydrogenation to afford the target standard compound.



Scheme 63: Successful synthetic route towards 65

To begin the SM investigation, a range of catalyst/ligand combinations were investigated at 5 mol% and 10 mol% respectively.

Table 6: Initial SM investigation into the effect of catalyst and ligand choice



65

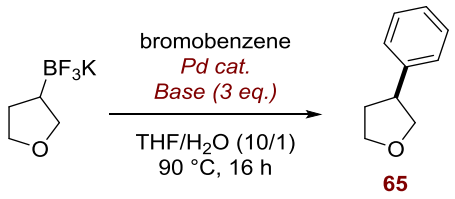
Catalyst → Ligand ↓	Conv. with $Pd(OAc)_2$ (%)[a]	Conv. with $PdCl_2$ (%)[a]	Conv. with $Pd_2(dba)_3$ (%)[a]	Conv. with $Pd(dba)_2$ (%)[a]	Conv. with $Pd(dppf)Cl_2$ (%)[a]	Conv. with $Pd(PPh_3)_4$ (%)[a]
No ligand	0	2	0	36[b]	11[d]	9[d]
DavePhos	8	0	0	0	-	-
XantPhos	5	14[b]	11[c]	11[c]	-	-
SPhos	5	8[c]	0	0	-	-
XPhos	2	4	3	3	-	-
RuPhos	0	6	4	4	-	-
PPh_3	1	3	1	0	-	-

a) Determined by HPLC using caffeine as internal standard b) further examination revealed result to be false positive; c) additional reaction with 10 mol% catalyst and 20 mol% ligand; d) additional reaction with 10 mol% catalyst

Following the initial screen, experiments with highest conversions were repeated with a view to obtaining isolated yields, however, further analysis showed no product formation (see results with superscript b). Interpretation of this screen was relatively ineffective, with no real pattern or obviously favourable catalyst or ligand evident. Several entries were performed using 10 mol% catalyst and 20 mol% ligand, but this did not increase the conversion past experimental error.

A small screen of bases was undertaken, employing a handful of common inorganic bases. There was found to be very little difference between each entry in this instance. Triethylamine was also utilised, but this provided no product.

Table 7: SM investigation into the effect of base using $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$.DCM



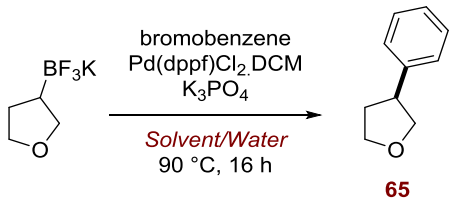
65

Entry	Catalyst	Base	Conversion (%)[a]
1	$Pd(PPh_3)_4$	$NaHCO_3$	10
2	$Pd(PPh_3)_4$	K_3PO_4	8
3	$Pd(PPh_3)_4$	K_2CO_3	9
4	$Pd(PPh_3)_4$	KO*t*Bu	2
5	$Pd(PPh_3)_4$	Et_3N	0
6	$Pd(dppf)Cl_2$.DCM	$NaHCO_3$	6
7	$Pd(dppf)Cl_2$.DCM	K_3PO_4	4
8	$Pd(dppf)Cl_2$.DCM	K_2CO_3	6
9	$Pd(dppf)Cl_2$.DCM	KO*t*Bu	1
10	$Pd(dppf)Cl_2$.DCM	Et_3N	0

a) Determined by HPLC using caffeine as internal standard

Next, the effect of solvent was investigated, in parallel with a water equivalents study. THF and dioxane were the only solvents which permitted any meaningful conversions and, at this stage, the equivalency of water did not have a pronounced effect.

Table 8: Investigation into the effect of water stoichiometry and solvent choice



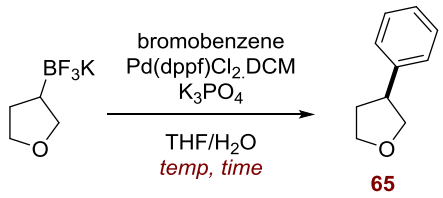
65

Solvent → Water (eq.) ↓	Conv. in THF (%)[a]	Conv. in Dioxane (%)[a]	Conv. in Toluene (%)[a]	Conv. in DMF (%)[a]	Conv. in Ethanol (%)[a]	Conv. in Ethyl Acetate (%)[a]
1	0	0	-	-	-	-
2	2	2	-	-	-	-
6	6	5	1	0	0	0
10	8	5	2	0	0	0
50	6	2	0	0	0	0
100	2	0	-	-	-	-

a) Determined by HPLC using caffeine as internal standard

The overarching observation with each reaction observed so far was the complex reaction profile. Despite there being only 2 or 3 UV-active components to the reaction, there were often in excess of 20 components observed by HPLC. This made accurate determination of the product peak and associated area difficult, and indicated that significant side-reactions were occurring. Milder reaction conditions were examined in an attempt to improve the overall reaction profile, through reducing temperature and time. However, this resulted in lower conversions, with no improvement to the reaction profile observed. In all cases, the levels of conversion increased with increasing time, ruling out the possibility that product was being transiently formed, and subsequently degraded.

Table 9: Investigation into the effect of time and temperature

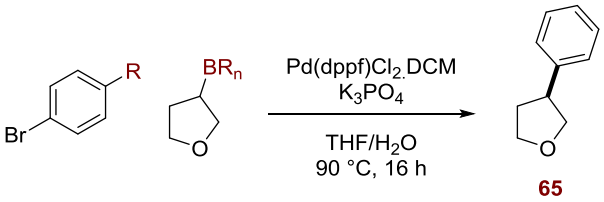


Temperature → Water (eq.) ↓	Conversion at 90 °C (%)[a]	Conversion at 50 °C (%)[a]	Conversion at rt (%)[a]
1	0	0	0
2	6	0	0
4	6	0	0
8	9	6	0
16	5	5	0

a) Determined by HPLC using caffeine as internal standard

Bromobenzene was replaced by a range of aryl bromides in an attempt to increase the rate of reductive elimination by making the ring more electron deficient. HPLC conversions were unable to be determined (due to the lack of requisite standard compound in each case), therefore TLC and ^{1}H NMR were used, but no product was observed for any aryl halide.

Table 10: Investigation into the effect of changing aryl halide and boron species



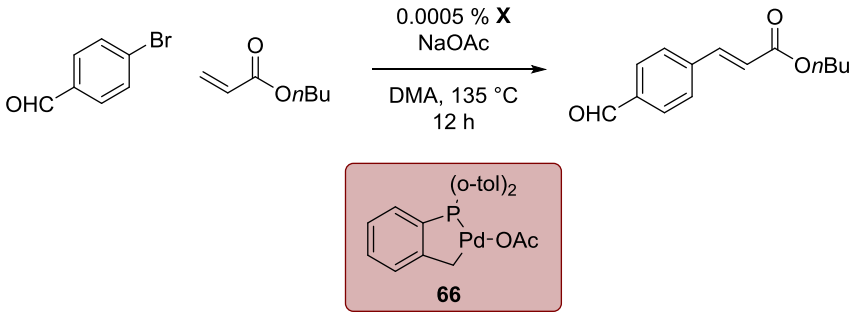
Entry	Boron Species	R	Conversion (%)[a]
1	BF_3K	NO_2	0
2	BF_3K	CO_2Me	0

3	BF_3K	CF_3	0
4	BPin	NO_2	0
5	BPin	CO_2Me	0
6	BPin	CF_3	0

a) Determined by HPLC using caffeine as internal standard

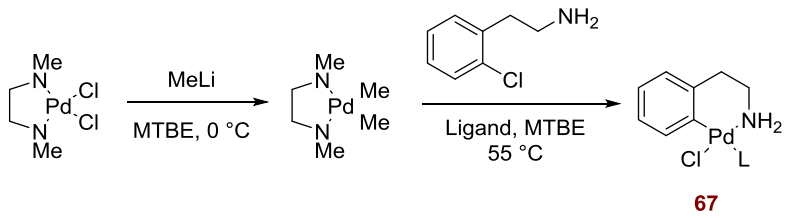
With no significant improvement being observed at this point, the application of precatalysts was investigated. Precatalysts have been shown to be particularly effective for troublesome SM reactions by increasing reaction rates.[181] In these systems, the ligand is bound to the palladium before reductive elimination provides the active catalyst.

The idea of precatalysts was first reported in 1995 by Herrmann and Beller to overcome some of the issues associated with generating active catalysts (reaction-impeding additives, difficulties in reducing Pd(II)).[182] They synthesised palladacycle **66** from the cyclometallation of $P(o\text{-tol})_3$ with $Pd(OAc)_2$. Unprecedented catalytic activity was observed in the Heck coupling outlined below; significantly more effective than the standard combination of $P(o\text{-tol})_3$ with $Pd(OAc)_2$.



Scheme 64: The first use of a palladium precatalyst in a cross-coupling by Herrmann and Beller

In the ensuing years, considerable interest in palladacycles for catalysis led to the discovery of a range of highly efficient precatalysts. In 2007, Buchwald and co-workers isolated a stable, primary amine-bound oxidative addition complex.[183] This finding inspired the development of the first 'Buchwald precatalyst' which had the ability to bear a range of phosphine ligands.[181] Treatment of this with base began the generation of LPd(0) *via* deprotonation and reductive elimination. These catalysts were found to be extremely effective in a variety of cross-coupling reactions, allowing transformations which were previously unable to be achieved using typical catalyst/ligand combinations.



Scheme 65: Generation of the first Buchwald precatalyst

Despite excellent improvements, these precatalysts suffered from several problems; namely, their inability to be deprotonated by weak bases at room temperature. By using 2-aminobiphenyl as the backbone, the amine was rendered more acidic, allowing deprotonation at room temperature by phosphate or carbonate bases.[184] This new series of catalyst was labelled 2nd generation. In 2013, the Buchwald group introduced 3rd and 4th generation precatalysts. The former were designed to be more stable in solution and to accommodate a greater range of ligands compared to previous generations – this was achieved by changing the counterion to a mesylate ion, rather than a chloride ion.[185,186] The 4th generation series also circumvented the formation of carbazole (which has been shown to inhibit cross-coupling), by methylating the amino group of the biphenyl backbone.[187]

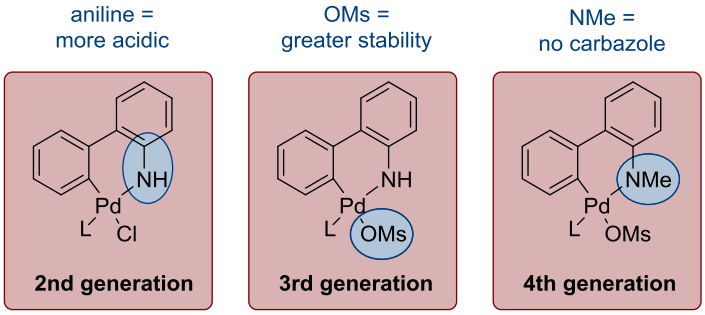
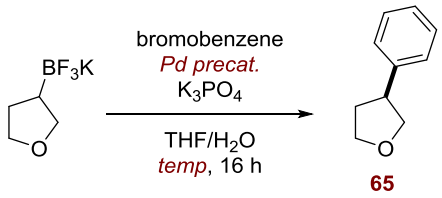


Figure 29: Buchwald's 2nd, 3rd and 4th generation precatalysts

Table 11: Initial investigations into the use of precatalyst in SM sp^2-sp^3 coupling



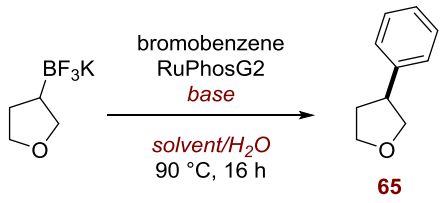
Entry	Precatalyst (10 mol%)	Temperature	Conversion (%)[a]
1	DavePhos G2	90	10

2	RuPhos G2	90	20, 21[b]
3	SPhos G2	90	5
4	XPhos G2	90	6
5	DavePhos G2	50	6
6	RuPhos G2	50	15
7	SPhos G2	50	0
8	XPhos G2	50	0

a) Determined by HPLC using caffeine as internal standard; b) 20 mol% catalyst used

As anticipated, the use of precatalyst systems improved the reactive outcome. RuPhos G2 provided the highest level of conversion to date, even at lower temperatures. The overall reaction profile (observed by HPLC) was also improved slightly. Based on this, RuPhos G2 was taken forward and subjected to a variety of further screening of reaction conditions.

Table 12: Investigation into variation of solvent, base and water stoichiometry whilst using RuPhosG2



65

Entry	Solvent	Water (eq.)	Base	Conversion (%)[a]
1	THF	6	K_3PO_4	0
2	THF	10	K_3PO_4	2
3	THF	20	K_3PO_4	13
4	Dioxane	6	K_3PO_4	0
5	Dioxane	10	K_3PO_4	2

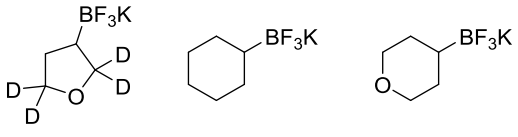
6	Dioxane	20	K_3PO_4	3
7	THF	6	K_2CO_3	0
8	THF	6	$NaHCO_3$	0

a) Determined by HPLC using caffeine as internal standard

The results in Table 12 show no increase in conversion through alteration of water equivalents. No product was observed when the base was changed to K_2CO_3 or $NaHCO_3$.

3.4.1 Conclusions and Outlook

At this point, work was halted on this section of research in conjunction with the beginning of investigation into a SM-hydrogenation protocol. A successful and scalable synthesis of a small range of racemic alkyl BF_3K salts has been developed, *via* a rhodium-catalysed hydroboration. An enantioselective variant was also developed, in moderate yields, but with excellent levels of enantioselectivity. Additionally, several useful chiral cyclic alkenes were synthesised with a view to being hydroborated. This reaction was unsuccessful, however, the enantioenriched systems could perhaps find use in other areas of chemistry in the future. The significant SM reaction investigation described above allowed conversion to reach greater than 20%, but this result was not bettered, and the reason for this has remained unclear. β-hydride elimination is a likely side-reaction, especially due to the particularly hydridic β-hydrogens on **26**. The product of this reaction was never observed directly though, perhaps due to its volatility. Replacement of the β-hydrogen atoms with deuterium atoms (and methyl groups) was attempted but a troublesome synthesis ceased these efforts (see **68**, below). Additionally, other BF_3K salts were used, but this did not have any beneficial effect on the outcome (see **69** and **70**). Future exploration of this reaction manifold may yield more successful results, however, at this time, efforts were focussed on a new approach to synthesise the chemical motifs of interest (*infra vide*).

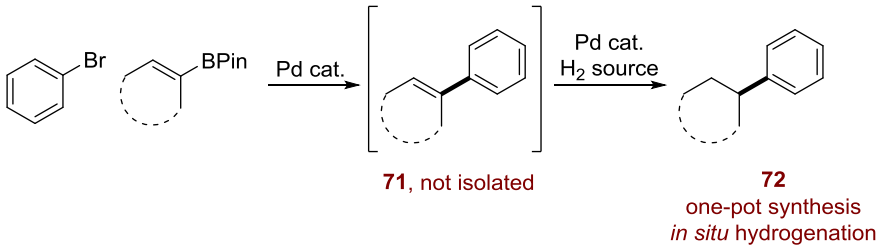


68 **69** **70**

Scheme 66: Attempted deuterated BF_3K 68, and other attempted BF_3K starting materials 69 and 70

3.5 Suzuki-Miyaura-Hydrogenation Using Hydrogen Gas

In consideration of the difficulties encountered in the previous section of work, an alternative cross-coupling approach was pursued. In this case, a single-pot SM-hydrogenation reaction was investigated. As illustrated in Scheme 67, it was envisaged that the coupling of a vinyl boron species with an aryl halide would provide intermediate **71**. Treatment of this transient styrenyl species with a hydrogen source could ultimately afford **72** in an efficient one-pot fashion.



Scheme 67: Generalised scheme of proposed SM-hydrogenation

This method represents a formal sp^2-sp^3 cross-coupling reaction and has the potential to avoid many of the familiar problems associated with the analogous sp^2-sp^3 SM reaction (the actual coupling event in this process is between two sp^2 hybridised centres). Firstly, the approach does not require the use of alkylboron species, whose instability has already been discussed. Alkenyl boronic acids and esters are also commercially available, unlike their alkyl counterparts. Secondly, sp^2-sp^2 SM cross-couplings have an exceptional functional group tolerance. It is the lack of generality associated with sp^2-sp^3 cross-couplings which makes them unfeasible, particularly within a medicinal chemistry setting. Finally, the reaction manifold outlined above could potentially be performed using common laboratory catalysts, allowing the use of complex and more bespoke precatalysts to be avoided.

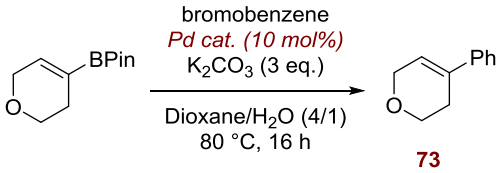
Although each single step in the Scheme 67 is known independently, the combination of two reactions into one single reaction vessel has a number of benefits. Chemical waste and overall time is decreased, whilst a work-up and purification step is avoided. The advantages of single-pot syntheses have been discussed previously.

3.5.1 Initial Optimisation

Preliminary studies began by investigating each step of the overall process independently. Reaction conditions for the cross-coupling of similar substrates were found and optimisation was performed from this starting point. Several common palladium catalysts were screened

initially, including the most common hydrogenation catalyst, Pd/C. A 91% conversion was achieved with 10 mol% Pd(dppf)Cl_2.DCM, and pleasingly, the loading could be lowered to 5 mol% with no detrimental effect. Pd/C performed less effectively, even at a higher catalyst loading. With such excellent conversion with Pd(dppf)Cl_2.DCM, no further catalysts were investigated at this time.

Table 13: Investigation into the effect of catalyst for SM reaction



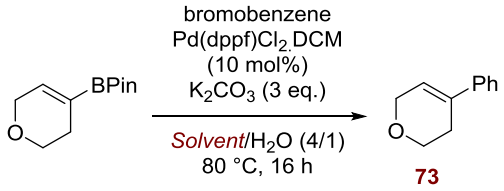
73

Entry	Catalyst	Conversion (%)[a]
1	$Pd(dba)_2$	6
2	$Pd(PPh_3)_4$	52
3	$PdCl_2$	15
4	Pd(dppf)Cl_2.DCM	91, 92[b]
5	Pd/C	36, 39[c]
6	$Pd_2(dba)_3$	70

a) Determined by HPLC using caffeine as internal standard b) 5 mol% catalyst used, c) 20 mol% catalyst used

Next, effect of solvent on the efficiency of the reaction was explored. THF, dioxane and toluene were chosen due to their frequent use in SM reactions, and EtOH and EtOAc due to their prevalence in hydrogenation reactions. Dioxane provided the highest conversion, with THF closely behind.

Table 14: Investigation into the effect of solvent for SM reaction



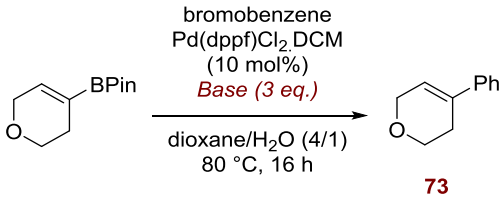
73

Entry	Solvent	Conversion (%)[a]
1	THF	80
2	Dioxane	89
3	Toluene	39
4	EtOH	57
5	EtOAc	50

a) Determined by HPLC using caffeine as internal standard

The effect of changing the base was found to be negligible, as shown in Table 15. Oven drying K_2CO_3 was also found to have no difference on conversion. In light of this, K_2CO_3 was taken forward as the base of choice. Penultimately, the stoichiometry of water was investigated, and a 20/1 ratio was identified as optimal (Table 16).

Table 15: Investigation into the effect of base for SM reaction



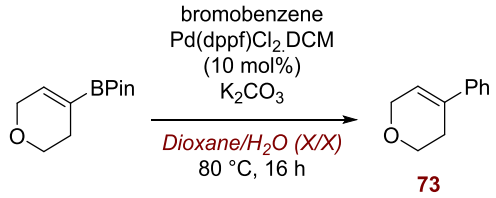
73

Entry	Base	Conversion (%)[a]
1	K_2CO_3	90
2	K_3PO_4	86
3	Cs_2CO_3	88

4	K_2CO_3 (dry)	88

a) Determined by HPLC using caffeine as internal standard

Table 16: Investigation into the effect of water stoichiometry for SM reaction

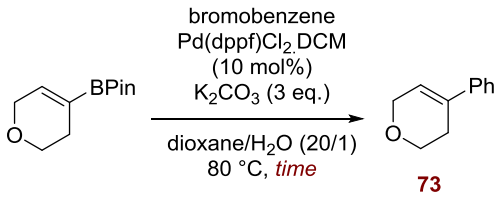


Entry	Water	Conversion (%)[a]
1	1 eq. (250/1)	51
2	5 eq. (50/1)	22
3	12.5 eq. (20/1)	92
4	50 eq. (4/1)	86
5	100 eq. (3/2)	90

a) Determined by HPLC using caffeine as internal standard

A brief time-study identified that the reaction was essentially complete after 2 hours (Table 17). However, when this was later applied to further substrates, 4 hours was required on some occasions. In an effort to make the reaction conditions as general as possible, 4 hours was therefore selected as the reaction time.

Table 17: Time study for SM reaction optimisation

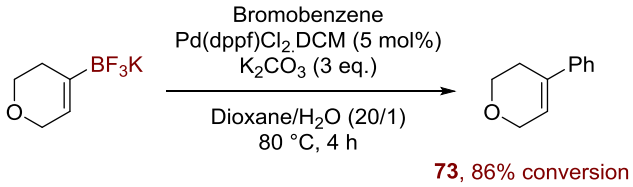


Entry	Time	Conversion (%)[a]
1	1 h	77

2	2 h	90
3	4 h	93
4	8 h	92
5	16 h	91

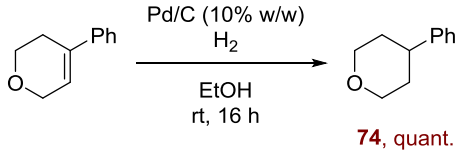
a) Determined by HPLC using caffeine as internal standard

An alternative boron species was utilised in Scheme 68, however, this had no beneficial effect on the reaction outcome. It does illustrate the tolerance of the reaction to a range of boron-based starting materials, though.



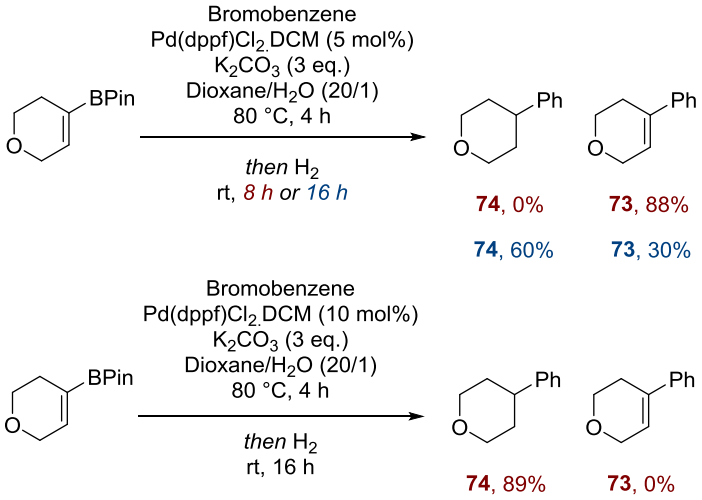
Scheme 68: SM reaction with BF_3K salt as starting material

With optimum SM conditions in hand, the hydrogenation reaction was attempted. Standard hydrogenation conditions using Pd/C in EtOH proved suitable and the desired product was attained in a quantitative yield.



Scheme 69: Hydrogenation of SM reaction product 73 using Pd/C and H_2

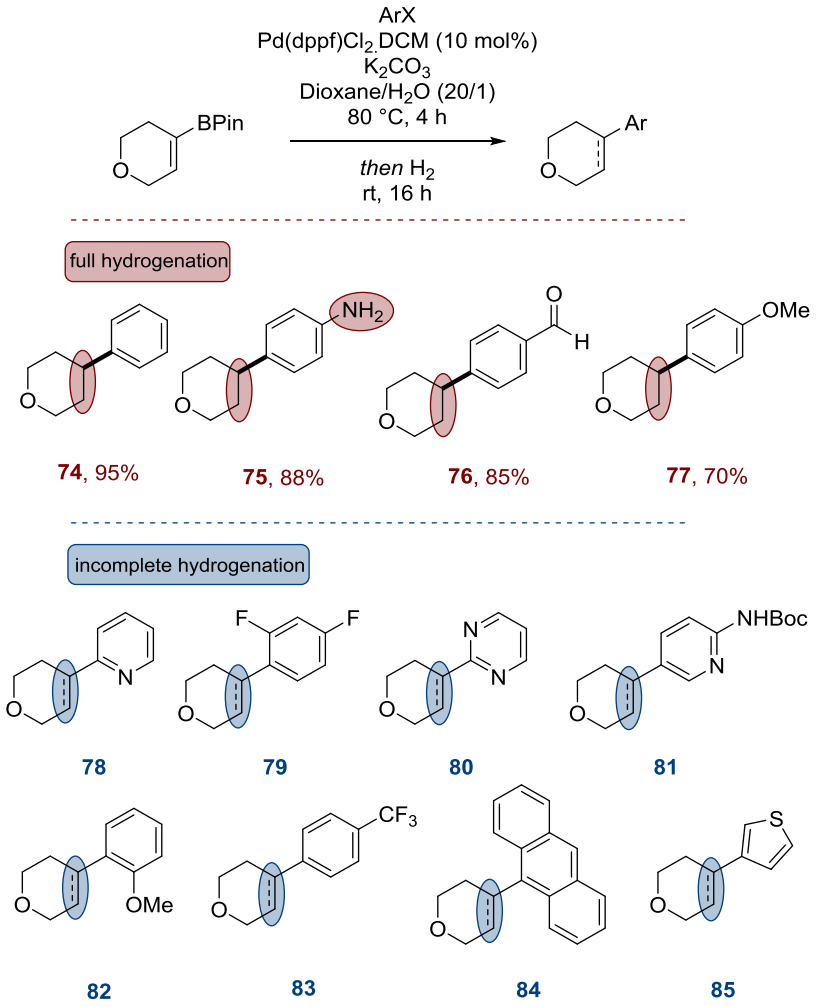
The next stage of study was to establish a protocol which would allow for both reactions to be performed in one pot. The SM reaction conditions were applied as above and after 16 hours, a balloon of hydrogen gas was added.



Scheme 70: Single-pot SM-hydrogenation with Pd(dppf)Cl₂.DCM as the sole palladium source

Initially, no reduction of olefin was observed, however when the duration of hydrogenation was increased, 60% of the isolated material was reduced. When the catalyst loading was increased to 10 mol%, full hydrogenation was achieved.

3.5.2 Exploration of Substrate Scope Using Optimised Conditions



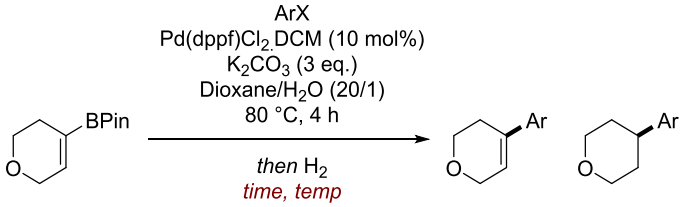
Scheme 71: Initial substrate scope for SM-hydrogenation reaction, with fully and partially hydrogenated substrates seperated

Following the brief optimisation campaign described above, exploration of the substrate scope was performed, which began in a promising manner. **74-77** were all isolated in good to excellent yields, with full hydrogenation in all cases. However, subsequent aryl halides examined were all unsuccessful in terms of hydrogenation. No conclusions regarding steric or electronic effects could be drawn from the emerging data, so the hydrogenation aspect of the emerging one-pot procedure was examined in more detail. It is important to note the SM element of each reaction occurred efficiently in each case.

3.5.3 Further Optimisation on Unsuccessful Substrates

Firstly, the influence of time and temperature was examined. Three aryl halides which exhibited no hydrogenation were selected for this investigation, however no improvement was found in increasing temperature, time or catalyst loading.

Table 18: Investigation into the effect of time, temperature and catalyst loading on hydrogenation reaction



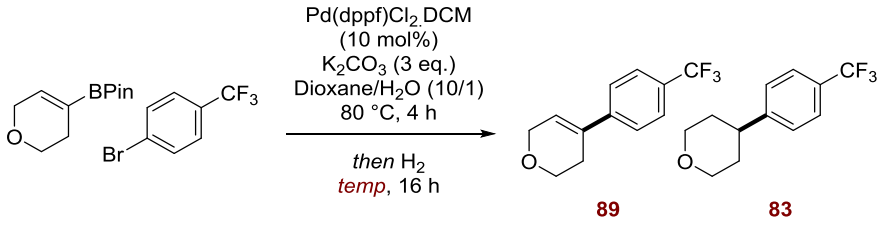
Entry	Aryl Halide	Temperature	Time (h)	Hydrogenation (%)[a]
1	86	rt	40	0, 0[b]
2	86	40 °C	16	0
3	86	60 °C	16	0
4	86	80 °C	16	0
5	87	rt	40	0[b]
6	87	40 °C	16	0
7	87	60 °C	16	0
8	87	80 °C	16	0
9	88	rt	40	0

10	88	40 °C	16	0
11	88	60 °C	16	0
12	88	80 °C	16	0

a) Determined by ^{1}H NMR; b) Reaction performed using 20 mol% Pd(dppf)Cl$_2$.DCM

Increased surface area is well documented to positively influence heterogeneously catalysed hydrogenation reactions.[188] With this in mind, attention turned to the use of new reaction vessels. All previous reactions within this project had been conducted in 0.5 – 2 mL microwave vials, which have a relatively low surface area. Larger microwave vials (2 – 5 mL) and round bottom flasks (RBF) (5 mL, 10 mL and 25 mL) were utilised.

Table 19: Investigation into the effect of vessel size on the SM-hydrogenation reaction

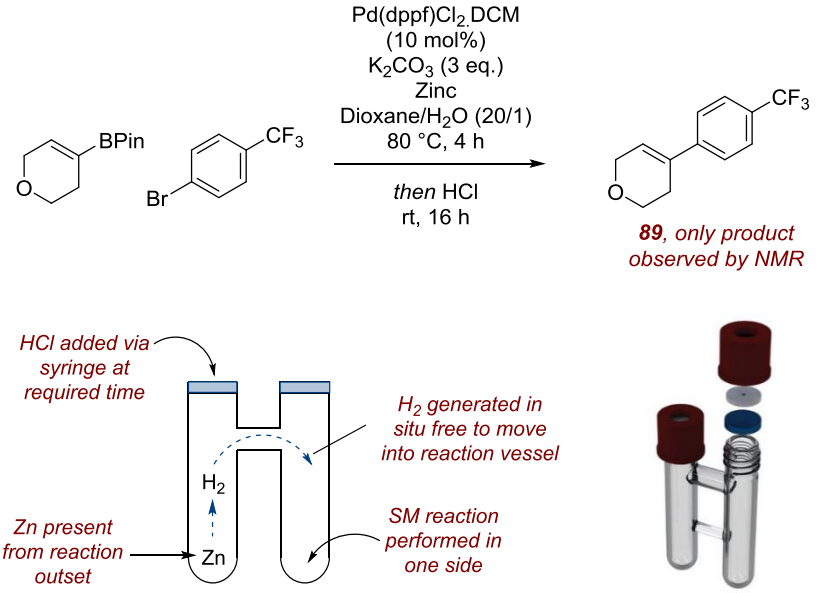


Entry	Reaction Vessel	Temperature	Hydrogenation (%)[a]
1	0.5 – 2 mL microwave vial	rt	0
2	2 – 5 mL microwave vial	rt	0
3	5 mL RBF	rt	0
4	10 mL RBF	rt	5
5	25 mL RBF	rt	10
6	25 mL RBF	40 ^{0}C	10
7	25 mL RBF	60 ^{0}C	10

As anticipated, larger reaction vessels (and therefore larger surface area) achieved a greater degree of hydrogenation. Despite these promising results, however, the extent of

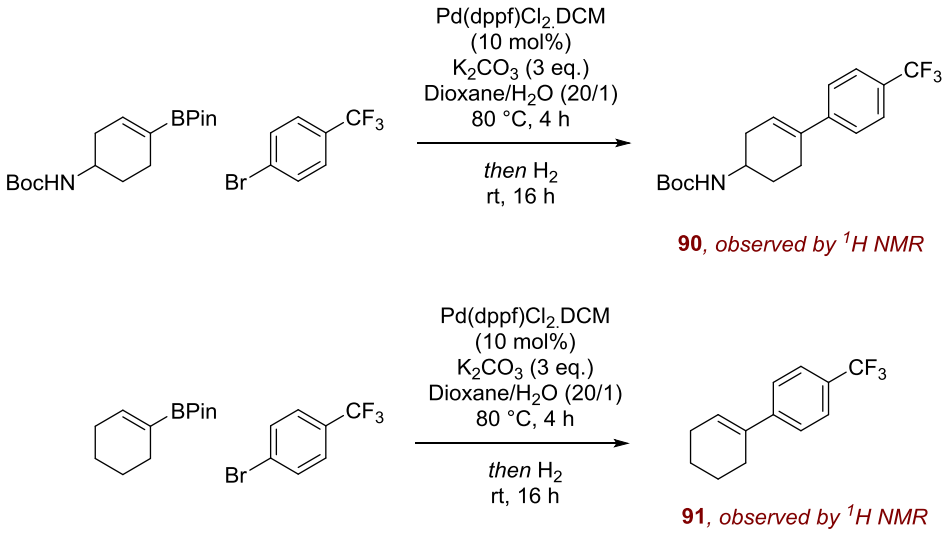
hydrogenation noted in Table 19 could not be increased by increasing the temperature. Due to physical constraints, the vessel size could not be further increased.

The reaction vessel was changed once more to a novel, dual chambered glass system known as COware which has been used for reactions which typically use carbon monoxide or hydrogen gas. The major advantage of COware (in relation to hydrogenation reactions) is that it avoids the direct use of hydrogen gas. In one chamber, the reaction is set up as usual (in this case, the SM reaction), whilst zinc filings are placed in the other chamber. At the desired time, a known volume of HCl is added, to generate a known amount of H_2 *in situ*. The system can also be sealed, allowing for pressure to be generated. The COware apparatus was implemented for the reaction shown in Scheme 72, however no hydrogenation was observed.



Scheme 72: Top, SM reaction performed using COware apparatus; bottom, explanation of COware

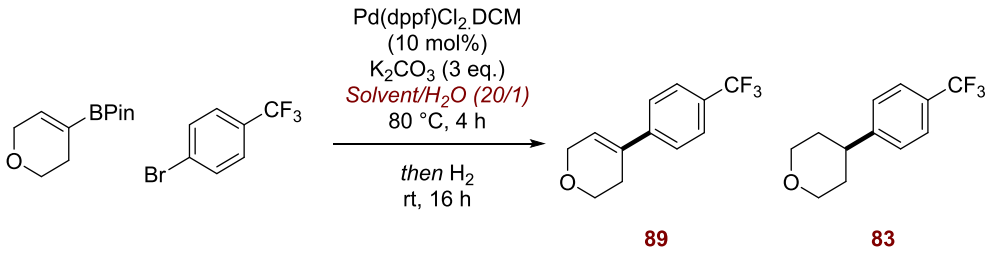
Although the choice of aryl halide had been varied, so far, the boronate pinacol ester used had remained constant. Two alternative boronate esters were applied to the reaction conditions shown in Scheme 73, however, no reduction of olefin was achieved in either case.



Scheme 73: Attempts at SM-hydrogenation using alternative alkenyl BPins

Solvent effect in hydrogenation reactions can be drastic, and this is due to the varying solubility of H_2 in different reaction media. Classically, alcohols (namely MeOH and EtOH) are used for Pd catalysed hydrogenation reactions due to the high solubility of H_2.[189] In light of this, Principal Component Analysis (PCA)[190] was used to identify a reaction solvent with similar properties to dioxane, but with an increased solubility of H_2. The solvents which suited this classification were *n*-butanol, 3-methyl-2-pentanone and ethyl acetate; however, hydrogenation was not achieved in any case.

Table 20: Investigation into the effect of solvent on hydrogenation

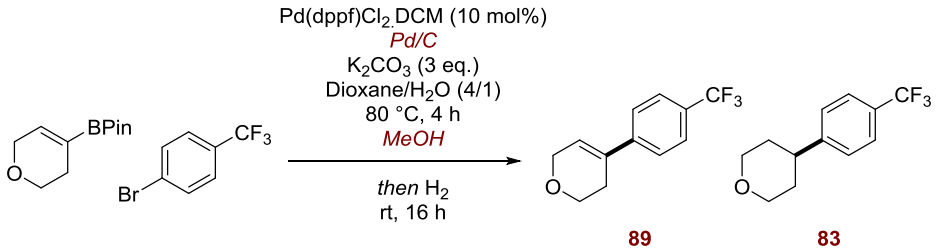


Entry	Solvent	Hydrogenation (%)[a]
1	*n*-butanol	0
2	3-methyl-2-pentanone	0
3	Ethyl acetate	0

a) Determined by ^{1}H NMR

In a similar vein, the addition of MeOH as a co-solvent was explored (Table 21). Various quantities of MeOH at different reaction points were added, with and without the inclusion of Pd/C as a co-catalyst, though no variation improved the reaction.

Table 21: Investigation into the effect of the addition of methanol at various time-points, along with the addition of Pd/C as a co-catalyst

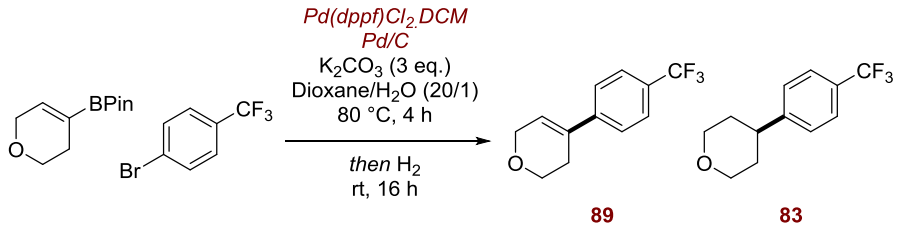


Entry	MeOH (mL)	MeOH addition time (h)	Pd/C (mol%)	Hydrogenation (%)[a]
1	0.2	0	-	0
2	1	0	-	0
3	0.2	4	-	0
4	1	4	-	0
5	2	4	-	0
6	0.2	0	10	0
7	1	0	10	0
8	0.2	4	10	0
9	1	4	10	0
10	2	4	10	0

a) Determined by ^{1}H NMR

Despite the lack of success in Table 21, efforts were focussed on investigating the addition of Pd/C as a co-catalyst. Variable amounts of Pd/C were included in the reaction, as well as increasing the Pd(dppf)Cl_2.DCM loading.

Table 22: Investigation into the effect of catalyst loading and Pd/C as a co-catalyst



89 83

Entry	Pd(dppf)Cl_2.DCM (mol%)	Pd/C (mol%)	Hydrogenation (%)[a]
1	15	0	0
2	20	0	0
3	0	20	100[b]
4	0	10	100[b]
5	5	5	0
6	10	10	0
7	20	20	0
8	2	18	90
9	5	15	90
10	1	9	90
11	2	8	0
12	3	7	0
13	4	6	0
14	5	15	0
15	2	10	10

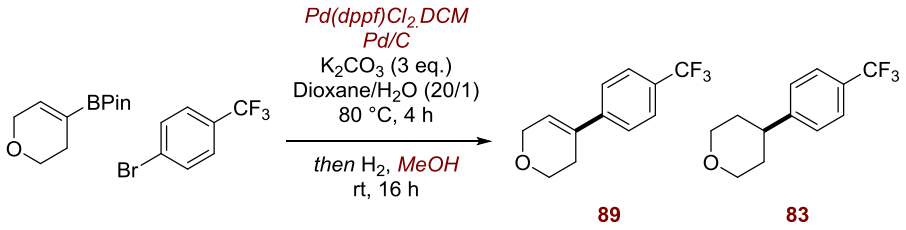
16	2	12	25
17	2	14	33
18	2	16	80
19	2	20	100

a) Determined by ^{1}H NMR; b) NMR showed <30% SM conversion

Unsurprisingly, when Pd/C was the only catalyst present, full hydrogenation occurred, but with low SM conversion. When the Pd(dppf)Cl_2.DCM and Pd/C were used concurrently, some success was observed. The ratio of the 2 catalysts appeared to have a substantial influence on the level of reduction: moving from 9:1 to 8:2 (Entry 10 vs Entry 11, Table 22) resulted in complete loss of hydrogenation. Pleasingly, at a ratio of 10:1 (Pd/C:Pd(dppf)Cl_2.DCM), complete hydrogenation was achieved – it is important to note that even with these low catalyst loadings, the SM aspect of the reaction also occurred almost quantitatively. Despite observing excellent conversion and full hydrogenation, a metal loading of 22 mol% was considered above an acceptable limit, and the use of methanol as a co-solvent was probed once again. When methanol was added at the point of hydrogen addition, this ratio could be lowered from 10:1 to 6:1 (Table 23, Entry 3).

It is theorised that the reason for the notable effect of ligand loading is due to the phosphine ligand blocking the catalytic Pd/C site. When the ligand content is too high, the palladium surface is obstructed, which inhibits the adsorption of hydrogen to the catalyst. This manner of catalyst poisoning has been previously observed with phosphorus[191] and sulfur.[192]

Table 23: Investigation into the effect of catalyst ratio on hydrogenation with MeOH addition



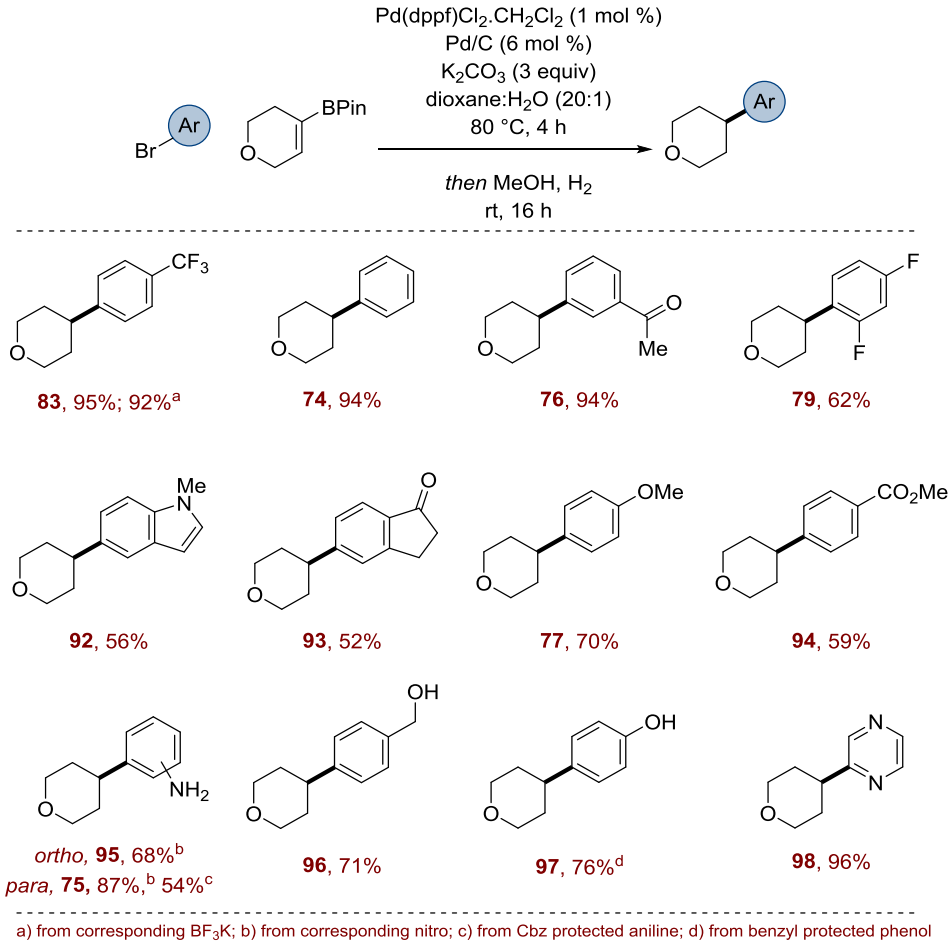
Entry	Pd(dppf)Cl_2.DCM (mol%)	Pd/C (mol%)	Hydrogenation (%)[a]
1	2	8	90
2	2	10	90
3	2	12	100, 29[b]
4	2	14	100
5	2	16	100
6	2	18	100
7	2	20	100
8	1	6	100

a) Determined by ^{1}H NMR; b) MeOH was replaced with additional dioaxane.

Entry 3 was performed with the addition of 1 mL of dioxane, rather than MeOH. A reduced level of hydrogenation was observed, indicating that the effect was (at least partially) due to an increased solubility of hydrogen, and not solely concentration driven. To reduce the overall catalyst loading further, the reaction was performed using 1 mol% Pd(dppf)Cl_2.DCM and 6 mol% Pd/C. Gratifyingly, full hydrogenation was observed with no significant drop in SM conversion.

3.5.4 Exploration of Substrate Scope Using Optimised Conditions

With optimised conditions in hand, the scope of the reaction was investigated again, firstly with respect to the aryl halide, using a pyranyl system as the boron species.



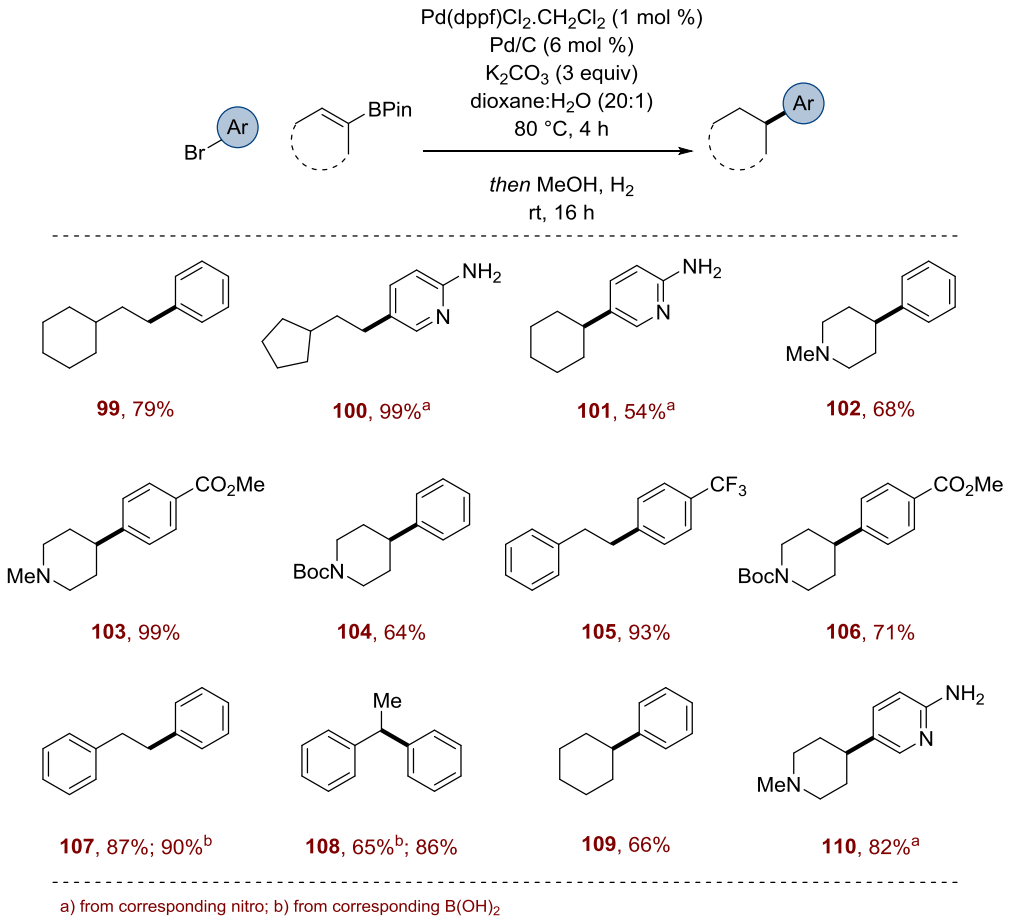
Scheme 74: Successful substrate scope with respect to aryl halides

In general, the nascent procedure was found to be applicable to a wide range of substrates, with good to excellent yields in almost all successful cases. As indicated in Scheme 74, 4-bromobenzotrifluoride coupled in excellent yields, using both the BPin and BF_3K derived boron species. Electron-neutral, electron-rich and electron-poor aryl halides were all well tolerated, with *ortho*, *meta*, and *para* substitution patterns examined. The reaction manifold was also compatible with heterocyclic substrates, which are highly attractive templates from a medicinal chemistry perspective as they are lead-like in terms of their physicochemical properties.[193]

Under the standard reaction conditions, complete hydrogenation was not attained for **77** or **79**. Increasing the temperature or time of the reductive step had no benefit, however, doubling the volume of MeOH lead to complete olefin reduction.

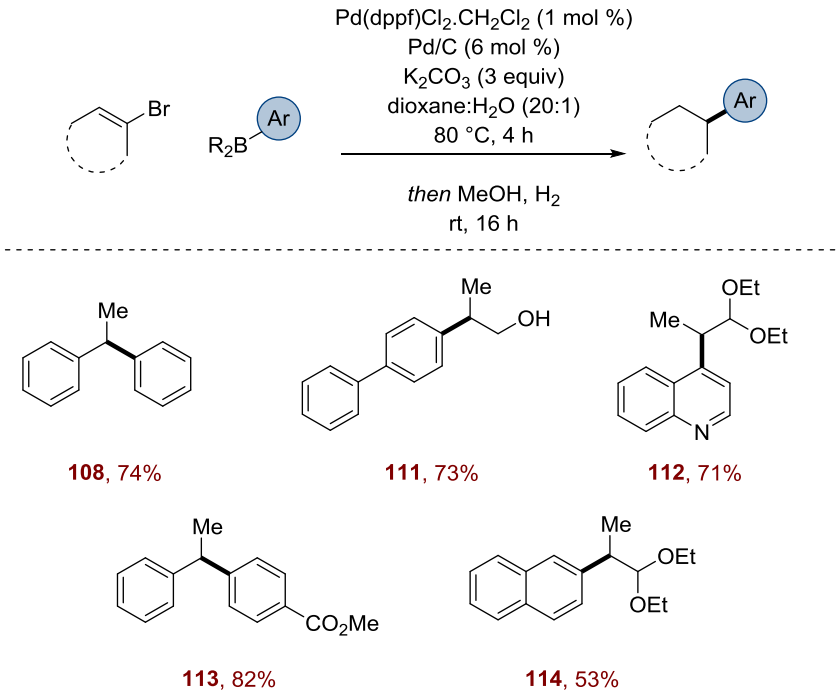
In another aspect of this part of the study, it was examined whether reducible groups or protecting groups labile to hydrogenolysis could be concomitantly transformed using the newly developed procedure. Entries **95** and **75** show that nitrobenzene derivatives can be reduced to the corresponding aniline system, while CBz protected amines and benzyl ethers could be removed under the reaction conditions, furnishing compounds **75** and **97**, respectively. These transformations are particularly advantageous as they avoid the need to couple free anilines or phenols, both of which can be problematic through poor oxidative addition and detrimental interactions with the palladium catalyst.

Having demonstrated the broad utility of the reaction for a range of aryl and heteroaryl halides, the scope of the vinyl boronate coupling partner was defined. A raft of both cyclic and acyclic alkenyl boronate esters and boronic acids were competent substrates for the reaction, providing the products in generally good to excellent yields as indicated in Scheme 75. Boc protected amines (**106**) and tertiary amines (**103**) proved to be amenable substrates, as did styrenyl based systems and amides. When a diene was used as one of the coupling partners, reduction of both olefins was observed to afford **99**. These examples also serve to illustrate how secondary alkyl systems can be formally cross-coupled in high fidelity without attendant issues of isomerisation.



Scheme 75: Successful substrate scope with respect to alkenyl boronate

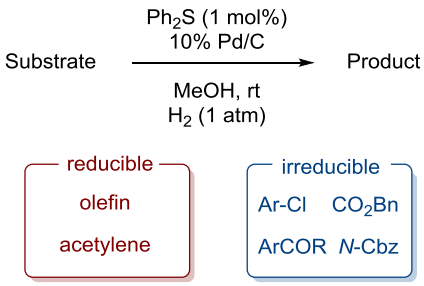
Satisfyingly, alkenyl bromides worked well as coupling partners with aryl boronic acids. A small set of compounds were synthesised, exhibiting good tolerance of alcohols, esters, ethers and heterocycles (Scheme 76).



Scheme 76: Successful substrate scope with respect to alkenyl bromide

3.5.6 Attempts at Olefin Selective Hydrogenation

Despite the advantageous manner of the dual reduction reactions, attempts were made to create an olefin-selective hydrogenation. In recent publication, Sajiki's group report the use of diphenyl sulfide to partially poison the catalyst, in order to inhibit certain hydrogenation reactions (Scheme 77).[192] This approach was examined in the newly developed procedure.

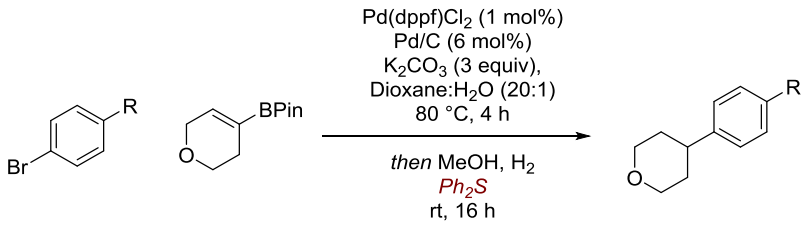


Scheme 77: Selective hydrogenation by Sajiki et al, using catalytic Ph_2S as a controlled catalyst poison

When this system was applied to the one-pot protocol, a selective hydrogenation was not achieved. In every case in Table 24, either olefin hydrogenation was inhibited, or the reaction profile exhibited an undeterminable mixture of by-products. It is likely that sulfur is inhibiting the function of Pd/C in a similar manner to the phosphine ligand. From optimisation, a 6:1 catalyst ratio is at the cusp of catalyst poisoning and increasing the loading of 'catalyst poison'

leads to incomplete olefin reduction. Accordingly, the loading of Pd/C was doubled, however this did not improve the reaction outcome. The concept of a selective hydrogenation was not investigated again until later in the project.

Table 24: Implementation of Sajiki's chemistry on the one-pot procedure under a range of conditions



Entry	Ph_2S (mol%)	Time of Ph_2S addition (h)	R	Yield
1	10	4	NHCbz	-
2	1	4	NHCbz	-, -[a]
3	10	0	NHCbz	-
4	1	0	NHCbz	-
5	10	4	OBn	-
6	1	4	OBn	-, -[a]
7	10	0	OBn	-
8	1	0	OBn	-

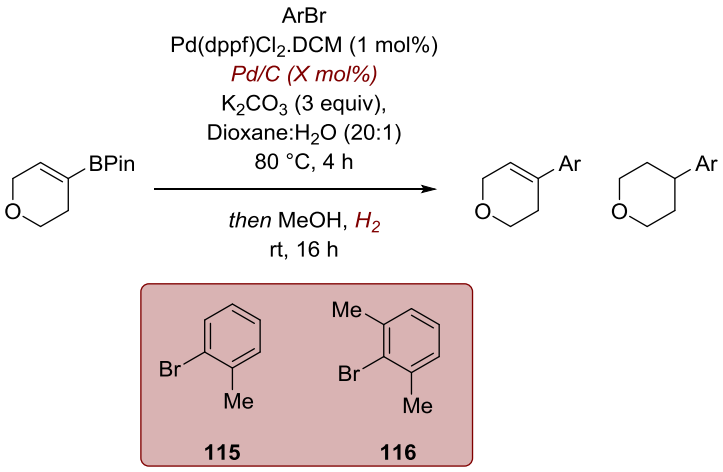
a) 12 mol% Pd/C used

3.5.7 Investigation into Increasing Hydrogen Pressure to Reduce *ortho* Substituted Aryl Halides

From the selection of substrates in Scheme 75, it is apparent that *ortho* substituents on the aryl halide were not widely tolerated. Fluorine atoms and nitro groups (or perhaps aniline at the point of olefin hydrogenation) were the only *ortho* functionalities successful under the standard reaction conditions. 2 unsuccessful aryl halides (2-bromotoluene **115** and 2,6-dimethylbromobenzene **116**) were utilised in pressurised hydrogenation reactions, using a

hydrogen bomb. Unfortunately, even at the hydrogen bomb's highest pressure (4 bar), the reduction was incomplete. Interestingly, the dimethylated aryl bromide experienced a greater level of olefin hydrogenation at every pressure.

Table 25: Investigation into increasing hydrogen pressure on sterically hindered substrates



Entry	Aryl Halide	Pd/C (mol%)	Hydrogen Pressure (bar)	% Hydrogenation[a,b]
1	115	6	Balloon, 1	0
2	116	6	Balloon, 1	0
3	115	10	Balloon, 1	0
4	116	10	Balloon, 1	0
5	115	6	2	0
6	116	6	2	0
7	115	10	2	15
8	116	10	2	23
9	115	10	3	34
10	116	10	3	39
11	115	10	4	42

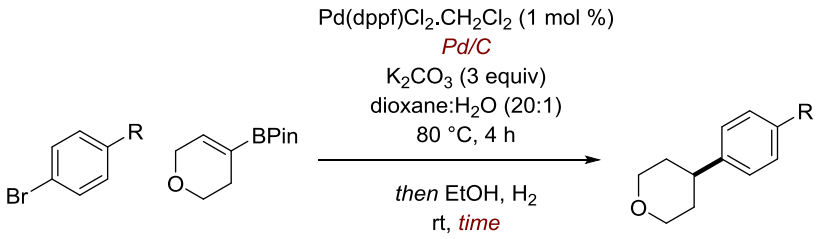
12	116	10	4	50

a) Determined by ^{1}H NMR; b) SM conversions were not recorded in this study

3.5.8 Investigation into the Replacement of Methanol with Ethanol

Due to the flammable nature of methanol, ethanol is regularly chosen as a solvent for hydrogenation reactions. As such, ethanol was used as a co-solvent in Table 26. This alteration was successful for bromobenzene, however, when the aromatic ring was functionalized, hydrogenation was suppressed. Increasing the Pd/C, ethanol and time proved successful for 4-bromobenzotrifluoride, although only 80% hydrogenation could be attained for 4-bromonitrobenzene.

Table 26: Examination of ethanol as a co-solvent

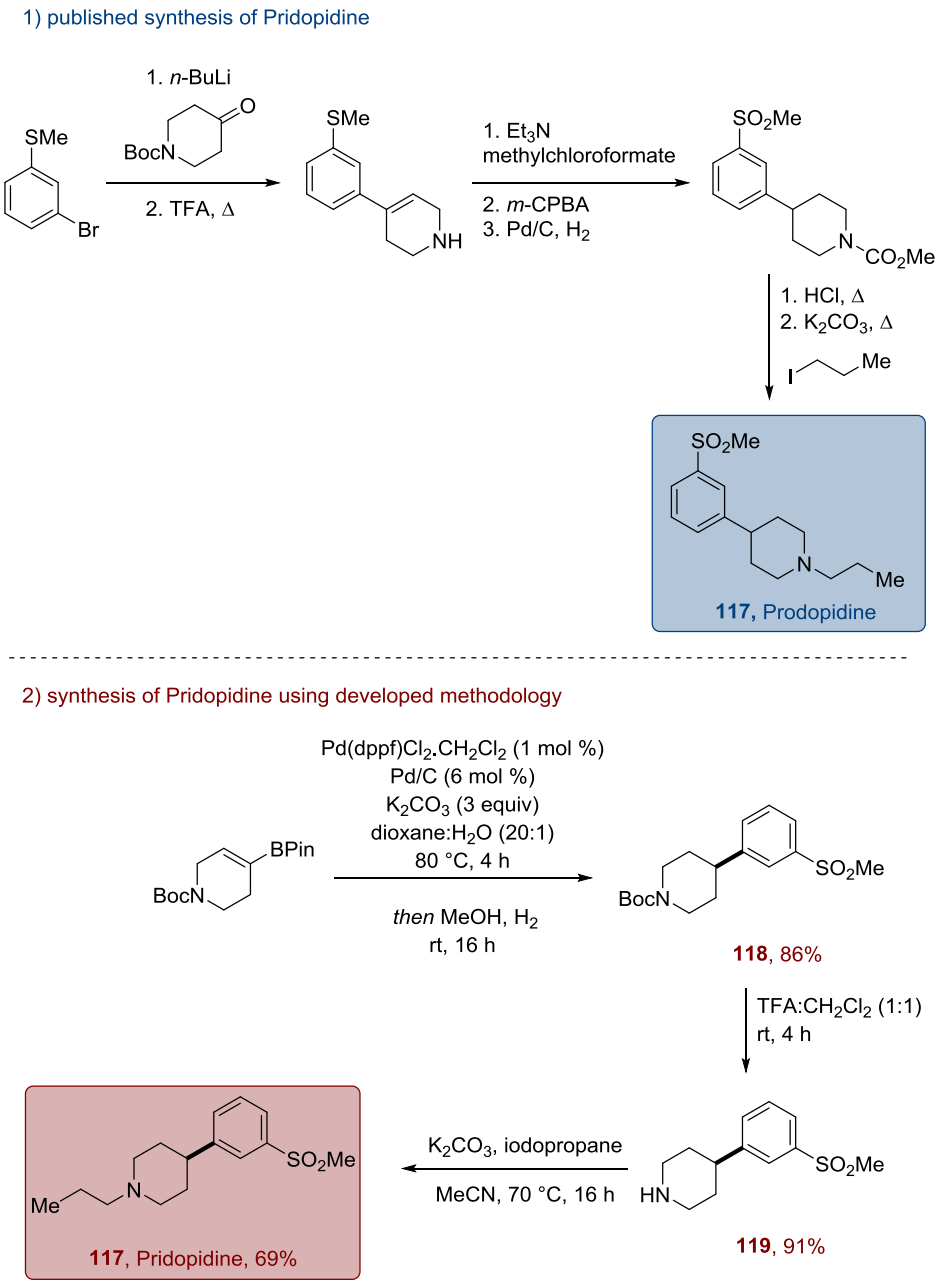


Entry	R	Pd/C (mol%)	EtOH (mL)	Time (h)	Hydrogenation (%)[a]	Yield
1	H	6	1	16	100	91%
2	CF_3	6	1	16	20	-
3	NO_2	6	1	16	50	-
4	CF_3	10	1	16	25	-
5	NO_2	10	1	16	55	-
6	CF_3	10	2	48	100	90%
7	NO_2	10	2	48	80	-

a) Determined by ^{1}H NMR

3.5.9 Application towards the Synthesis of Pridopidine

To illustrate the relevance of the method within medicinal chemistry, the synthesis of a biologically active compound was explored. For this aspect of the study, Pridopidine, a dopaminergic antagonist currently undergoing phase III clinical trials for the treatment of Huntingdon's disease, was chosen as the target of interest.[194] The synthetic approach involved the application of the newly developed method in the first step, followed by a Boc-deprotection and subsequent alkylation. The SM-hydrogenation proceeded cleanly in an 86% yield. Application of this emerging approach reduces the overall length of the synthesis of Pridopidine by 4 steps compared to the previously disclosed route, highlighting the effectiveness of the current study in the context of target molecule synthesis.[195]



Scheme 78: 1) Published synthesis of Pridopidine 2) Application of developed methodology in the synthesis of Pridopidine

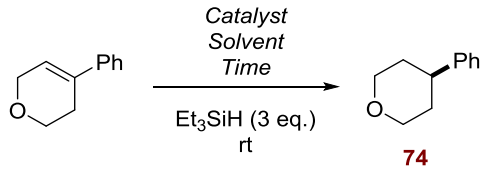
3.6 Suzuki-Miyaura-Transfer-Hydrogenation (SM-TH)

With an efficient protocol utilising gaseous hydrogen in hand, an equivalent approach which bypassed the use of hydrogen gas was subsequently investigated. There are inherent dangers associated with the use of hydrogen gas and, as with any flammable agent, difficulties can arise when scale is increased, particularly at a process level.

3.6.1 Initial Optimisation of a SM-TH Protocol

To circumvent these issues, a transfer-hydrogenation protocol was explored (Table 27). Pleasingly, triethylsilane was found to be efficient at reducing **73** in a range of solvents, with extremely short reaction times. As observed with the previous methodology, Pd(dppf)Cl_2.DCM was unable to effectively act as a hydrogenation catalyst (Entries 3 & 4), so Pd/C was again employed as a co-catalyst.

Table 27: Initial investigation into TH reaction using triethylsilane

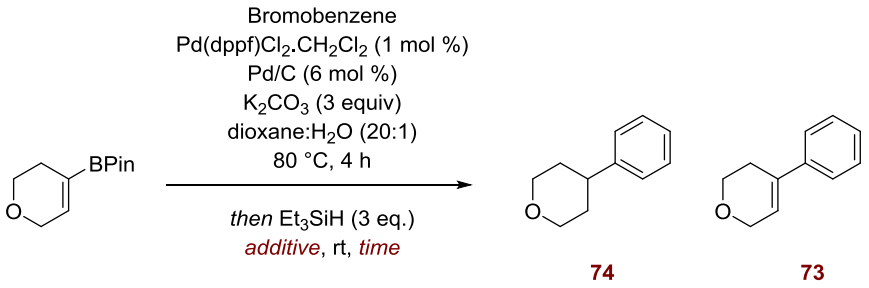


Entry	Catalyst	Loading (mol%)	Solvent	Time	Hydrogenation (%)[a]
1	Pd/C	10	MeOH	16 h	100
2	Pd/C	5	MeOH	16 h	100
3	Pd(dppf)Cl_2.DCM	1	MeOH	16 h	0
4	Pd(dppf)Cl_2.DCM	5	MeOH	16 h	16
5	Pd/C	6	Dioxane	16 h	100
6	Pd/C	6	Dioxane	30 min	100
7	Pd/C	6	Dioxane	5 min	100
8	Pd/C	6	Dioxane	3 min	100
9	Pd/C	6	Dioxane	1 min	87

a) Determined by ^{1}H NMR

The results shown in Table 28 did not correlate directly when applied to the one-pot procedure, however. The rate of reaction was severely reduced, and the addition of MeOH was again necessary.

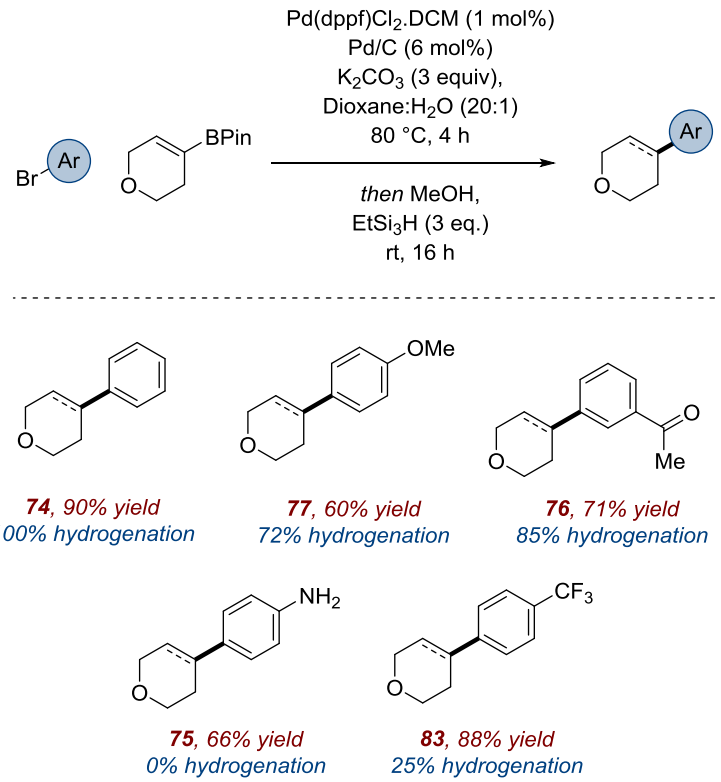
Table 28: Application of transfer hydrogenation to one-pot procedure



Entry	Additive	Time	Hydrogenation (%)[a]
1	MeOH	16 h	100
2	-	16 h	0
3	MeOH	1 h	0
4	EtOH	16 h	0

a) Determined by ^{1}H NMR

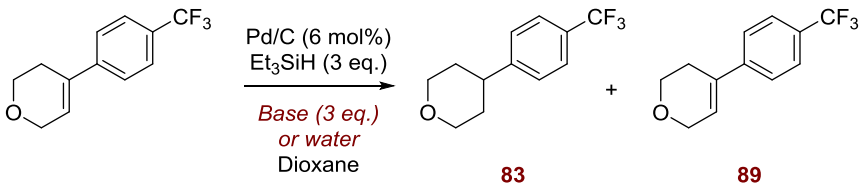
Unfortunately, the reaction conditions were subsequently not found to be general with the small substrate set outlined in Scheme 79. Although the yields were generally good, the extent of hydrogenation varied dramatically in each case.



Scheme 79: Application of one-pot SM-TH reaction with various aryl halides

In consideration of these mixed results, an unsuccessful substrate (**83**) was used for further optimisation of hydrogenation conditions. Investigation into the reaction temperature, catalyst loading and volume of methanol yielded no improvement to the rate of hydrogenation therefore. Concurrently, an exploration into the effect of base and water was performed to delineate the influence of each reaction component (Table 29).

Table 29: Investigation into the effect of base and water on the TH aspect of the reaction



Entry	Base/H_2O	Hydrogenation (%)[a]
1	K_2CO_3	24
2	K_2CO_3	22
3	K_3PO_4	25

4	Na_2CO_3	55
5	$CaCO_3$	100
6	Cs_2CO_3	0
7	NaOH	28
8	Et_3N	12
9	Water (no base)	100

a) Determined by ^1H NMR

Generally, the effect of base did not alter significantly within the screen. With the exception of $CaCO_3$, every base had a significant detrimental effect on the hydrogenation reaction. As Entry 9 shows, water had no effect on the reaction.

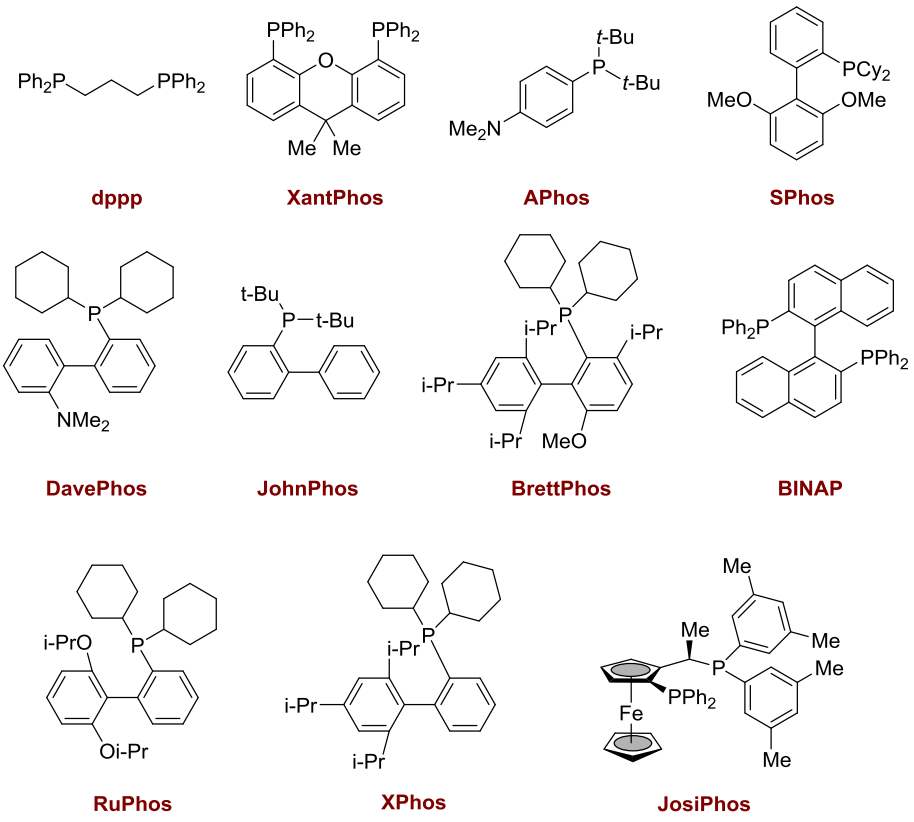
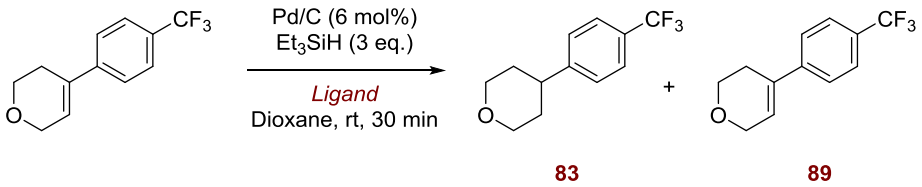


Figure 30: Ligands employed in transfer hydrogenation ligand screen

Table 30: Investigation into the effect of added ligand to the transfer hydrogenation



83 89

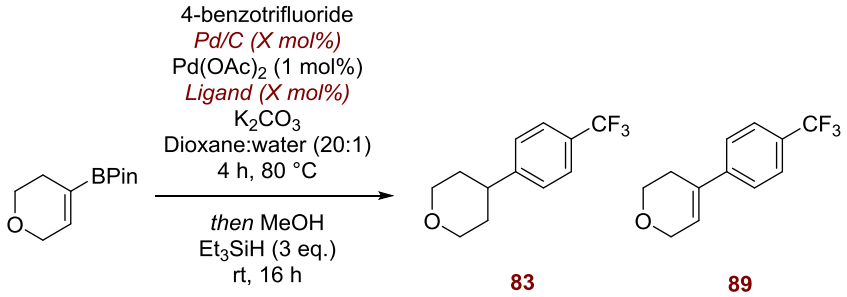
Entry	Ligand	Loading (mol%)	Hydrogenation (%)[a]
1	Pd(dppf)Cl_2.DCM	1	83
2	Pd(dppf)Cl_2.DCM	12	44
3	dppf	1	93
4	dppf	12	8
5	dppf	3	30
6	DavePhos	3	100
7	JohnPhos	3	100
8	BrettPhos	3	100
9	RuPhos	3	100
10	XPhos	3	100
11	BINAP	3	85
12	JosiPhos	3	78
13	XantPhos	3	63
14	dppp	3	0
15	APhos	3	66
16	SPhos	3	66

a) Determined by ^{1}H NMR

A series of common commercial phosphine ligands was tested in the reaction, shown in Figure 30 and Table 30. Nearly all of these inhibited the hydrogenation reaction, most likely by coordinating to the palladium surface and reducing the surface area available for hydrogen adsorption, as described before. From the screening experiment, there were 5 compatible ligands: DavePhos, JohnPhos, BrettPhos, RuPhos and XPhos. Notably, monodentate ligands performed better compared with bidentate ligands. BINAP was the only exception to this; however, due to the steric bulk surrounding the two phosphine atoms, they are possibly less able to detrimentally interact with the palladium catalyst.

Three of the successful ligands were applied to the one-pot process and the results are shown in Table 31. Despite the negative influence of the ligand being more pronounced in this procedure, full hydrogenation was achieved when 10 mol% Pd/C was used (Entries 6 and 7).

Table 31: Application of successful ligands to the one-pot, two-step process



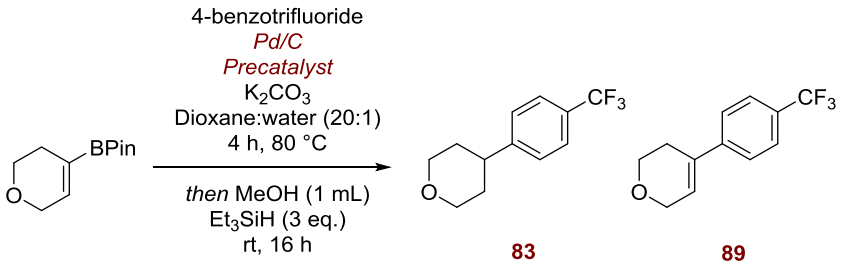
Entry	Ligand	Ligand Loading (mol%)	Pd/C Loading (mol%)	Hydrogenation (%)[a]
1	BrettPhos	2	6	22
2	XPhos	2	6	62
3	RuPhos	2	6	28
4	XPhos	2	6	-[b]
5	RuPhos	2	6	59
6	XPhos	2	10	100
7	RuPhos	2	10	100
8	XPhos	1	6	79

9	RuPhos	1	6	56

a) Determined by ^{1}H NMR; b) Unable to determine extent of hydrogenation by ^{1}H NMR

The number of reactants present in the conditions in Table 31 was considered excessive, therefore precatalysts were also considered to reduce the overall reactant loading.

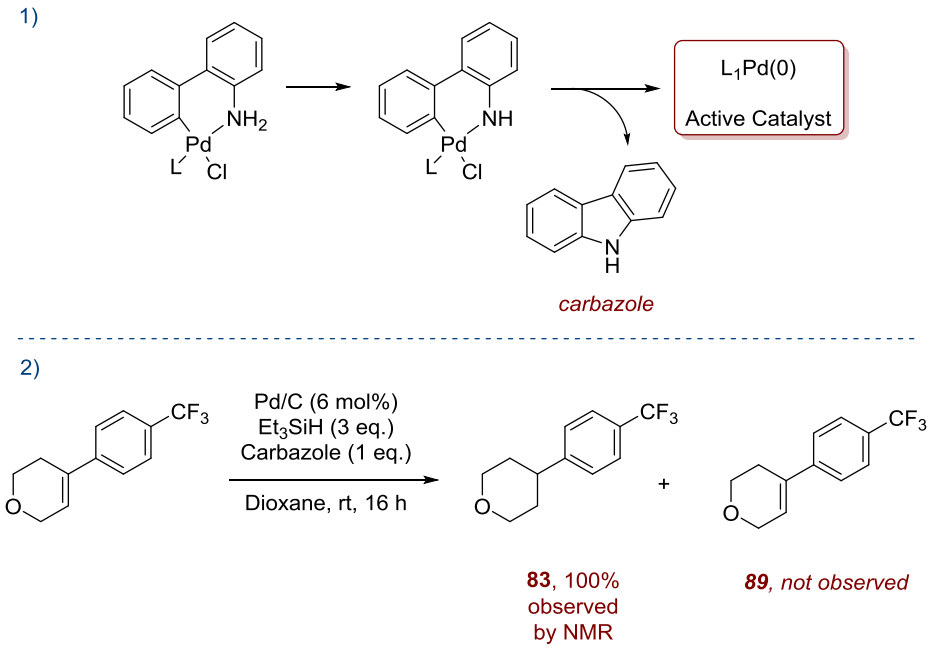
Table 32: Application of precatalysts to the one-pot, two-step process



Entry	Precatalyst	Pd/C Loading (mol%)	Hydrogenation (%)[a]
1	Xphos G2	6	41
2	RuPhos G2	6	26
3	BrettPhos G3	6	36
4	Xphos G2	10	61
5	RuPhos G2	10	30
6	BrettPhos G3	10	62

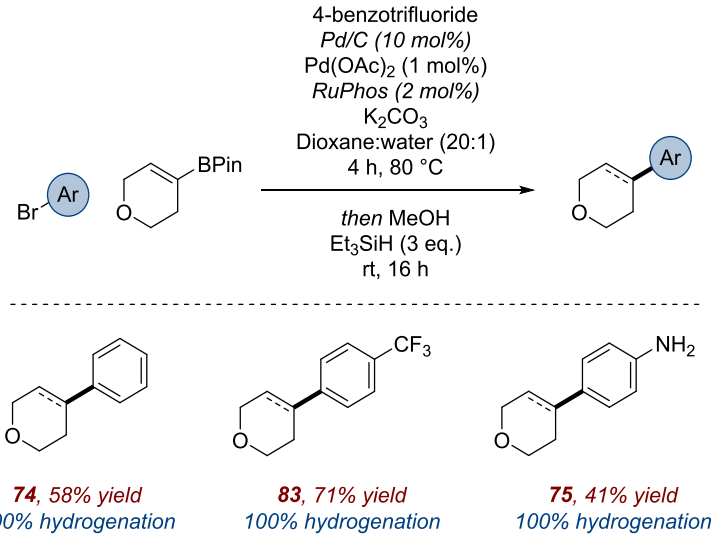
a) Determined by ^{1}H NMR

Surprisingly, the precatalysts impeded the transfer hydrogenation more than their unbound ligand counterparts. It was hypothesised that the inhibition was due to the byproduct formed in the activation of the precatalyst. As shown below, deprotonation followed by reduction elimination forms the active Pd(0) catalyst, with the emission of carbazole, which has been previously reported to hinder palladium-catalysed reactions.[196] Having stated this, addition of an equivalent of carbazole to the hydrogenation reaction was found to have no inimical effect (Scheme 80).



Scheme 80: 1) Mechanism of activation of precatalysts; 2) the addition of carbazole to transfer hydrogenation

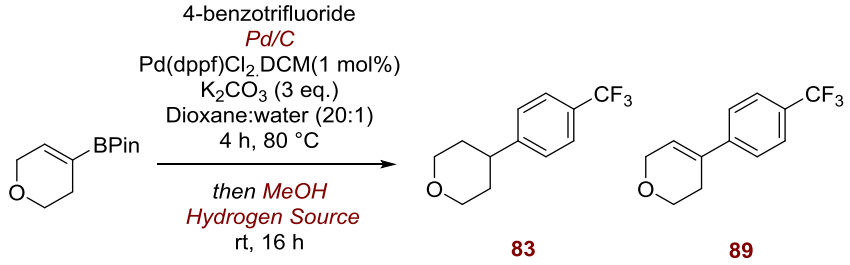
A cursory exploration of the generality of reaction conditions chosen from Table 31 found the conversion to product to be sub-optimal. To this point, the only aspect of consideration was the degree of hydrogenation by ^{1}H NMR, and not the yield of the SM reaction.



Scheme 81: Cursory scope exploration using optimised reaction conditions from Table 31

The difficulty in this situation was that to increase the conversion, the quantities of both ligand and catalyst needed to be increased, which would result in inhibition of hydrogenation. As such, the hydrogen source was briefly reviewed and ammonium formate was found to ameliorate the previous choice under the original SM conditions.

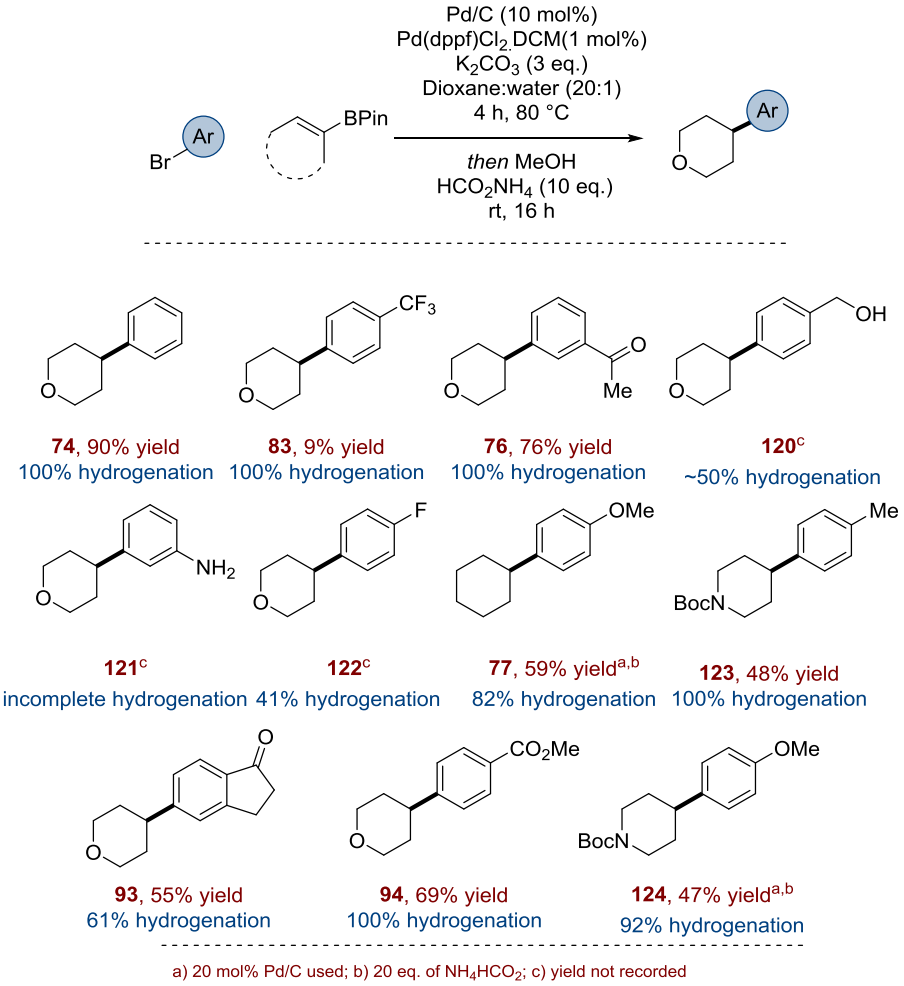
Table 33: Catalyst loading and hydrogen source investigation



Entry	Hydrogen Source	Pd/C Loading (mol%)	MeOH (mL)	Hydrogenation (%)[a]
1	Et_3SiH	15	1	72
2	Et_3SiH	20	1	76
3	Et_3SiH	20	2	100
4	HCO_2NH_4	10	1	57
5	HCO_2NH_4	10	2	100

a) Determined by ^1H NMR

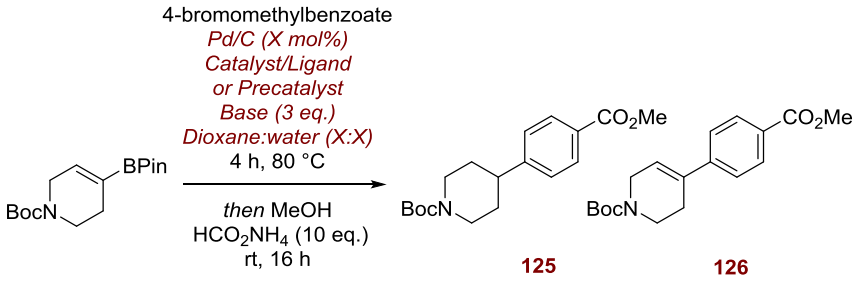
Similarly to before, these conditions were not general. For unsuccessful substrates, increasing the amount of Pd/C and ammonium formate improved the degree of hydrogenation in some cases, but this no longer represented a general method towards the compounds of interest. Based on the ligand screen (Table 31), the catalyst system which provided the cleanest reaction profile was selected (XPhos) for further screening.



Scheme 82: Application of developed SM-TH conditions to a range of aryl bromides and alkenyl BPins

A brief optimisation of previous conditions found that to achieve a reasonable SM conversion, an XPhos loading of 4 mol% was required (Table 34). Pleasingly however, a higher yield could be attained using the equivalent XPhos precatalyst. Using these conditions, full hydrogenation could also be accomplished with 12 mol% Pd/C. Due to problems with chemical supply, the optimisation was performed on a different alkenyl BPin, however these results were later confirmed to be reproducible on pyran derived Bpin. Further optimisation (Entries 9-10) found that base choice and water content had to be optimised to achieve optimal reaction conditions.

Table 34: Significant examples of further optimisation of SM-TH conditions



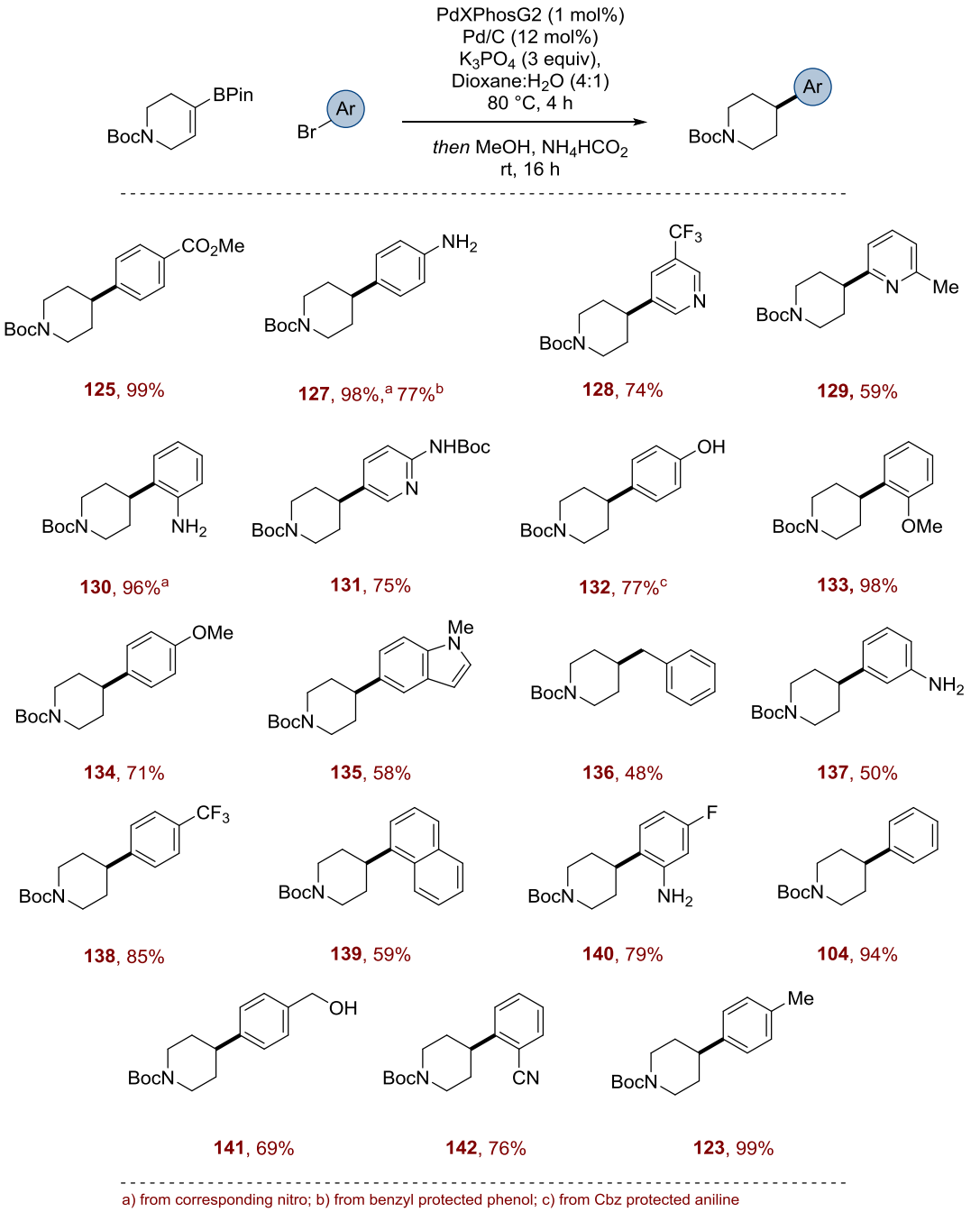
Entry	Catalyst/Precatalyst (mol%)	Pd/C Loading (mol%)	Base	Dioxane:H_2O	125:126[a]	Yield (%)
1	$Pd(OAc)_2$/XPhos (1, 2)	10	K_2CO_3	20:1	18:72	38
2	$Pd(OAc)_2$/XPhos (2, 4)	20	K_2CO_3	20:1	24:76	51
3	$Pd(OAc)_2$/XPhos (2, 4)	20	K_2CO_3	20:1	-[c]	50
4	$Pd(OAc)_2$/XPhos (3, 3)	20	K_2CO_3	20:1	43:57	83
5	$Pd(OAc)_2$/XPhos (4, 4)	20	K_2CO_3	20:1	43:57	89
6	XPhos G2 (1)	8	K_2CO_3	20:1	53:47	-[b]
7	XPhos G2 (1)	10	K_2CO_3	20:1	80:20	-[b]
8	XPhos G2 (1)	12	K_2CO_3	20:1	100:0	81
9	XPhos G2 (1)	12	K_3PO_4	20:1	100:0	90
10	XPhos G2 (1)	12	K_3PO_4	4:1	100:0	>99%

a) Determined by ^1H NMR; b) not isolated; c) unable to determine ratio

3.6.2 Exploration of Substrate Scope

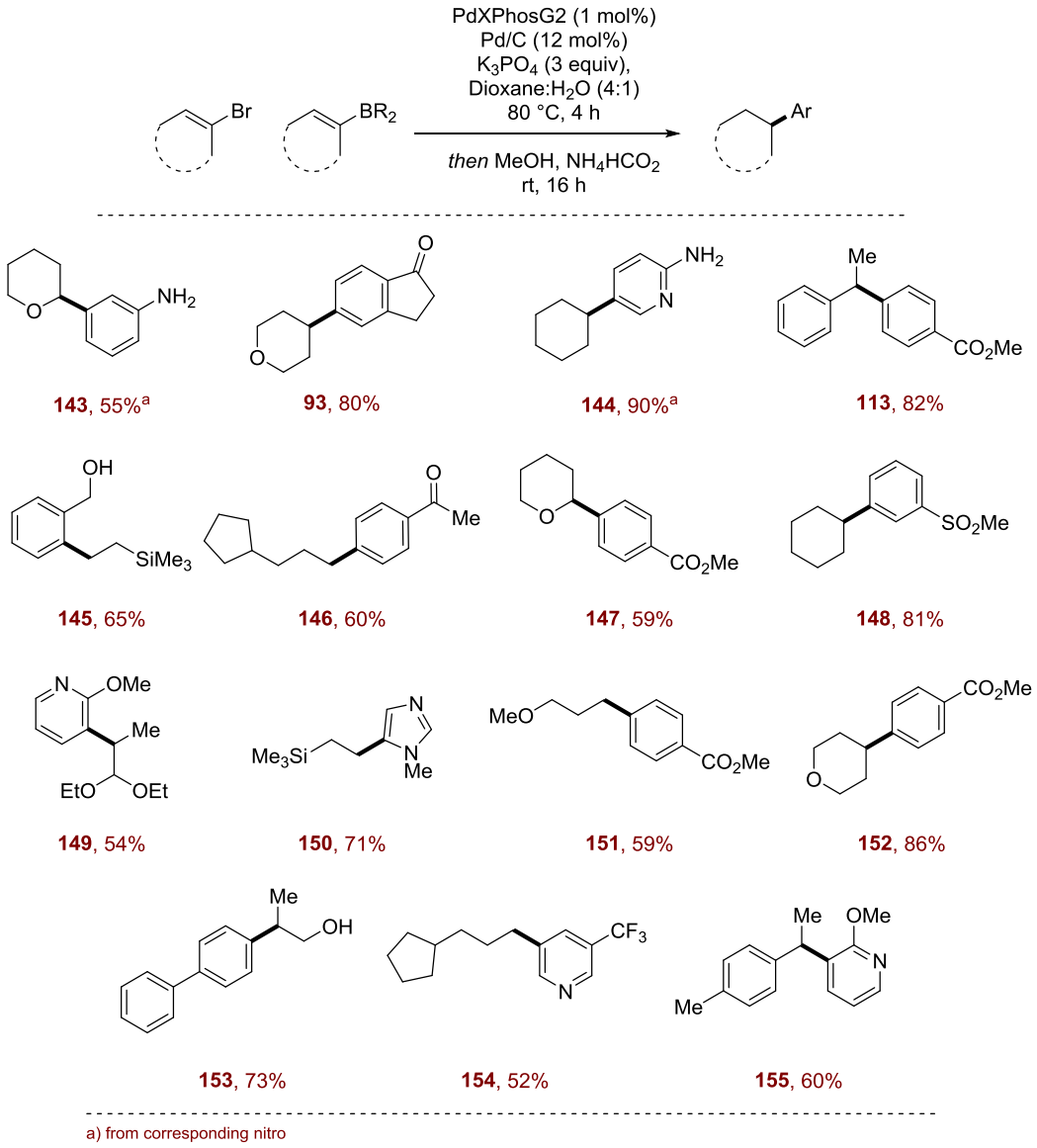
With optimal conditions in hand (Table 34, Entry 10); the generality of the reaction was investigated, firstly with respect to the aryl halide. Using the dihydropyridine BPin, a plethora of aryl bromides were found to be tolerable to the reaction conditions. As can be noted from Scheme 83, electron-withdrawing and electron-donating groups worked well, as did several hetereocycles. Benzyl bromide reacted in moderate yields, providing an example of a formal

sp^3-sp^3 coupling. As observed with the gaseous adaption of this reaction, hydrogen labile groups were reduced – these included nitro groups, Cbz protected anilines and benzyl protected phenols however, the nitrile group in example **142** remained intact. In contrast to using hydrogen gas, several *ortho* substituted aryl bromides were successfully coupled and reduced (**130**, **133** and **142**).



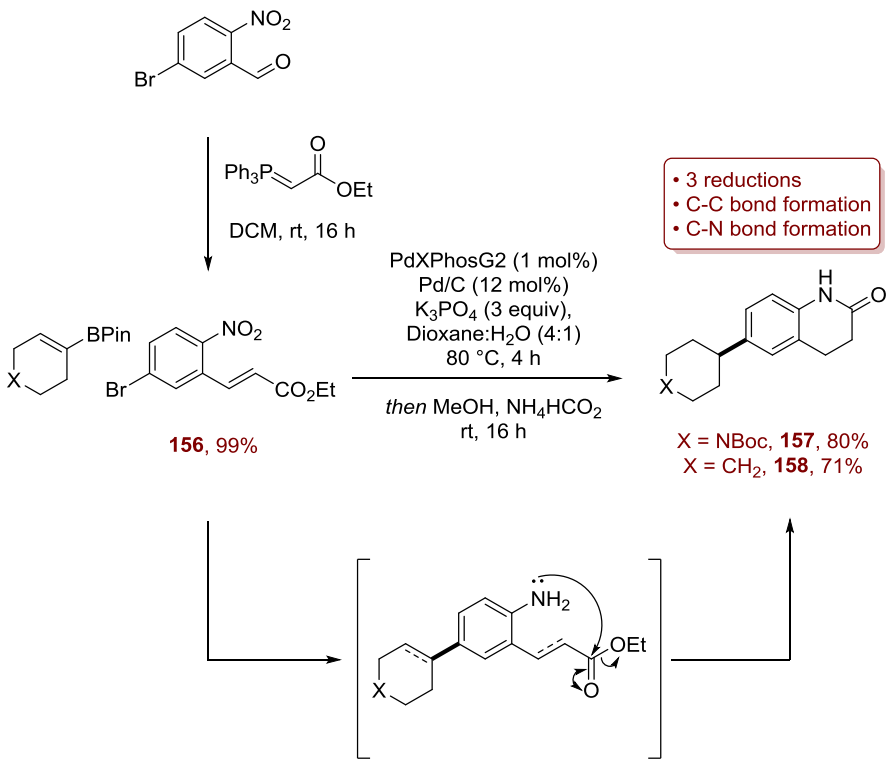
Scheme 83: Successful substrate scope with respect to aryl halides

The scope of reaction was extended to include a variety of alkenyl bromides and boronate esters. This survey demonstrated the exceptional functional group tolerance of the newly developed reaction, allowing a facile approach to molecules with fragment- and lead-like properties. Yields ranged from good to excellent, and compounds were accessed that one might expect to be difficult to make using current synthetic procedures.



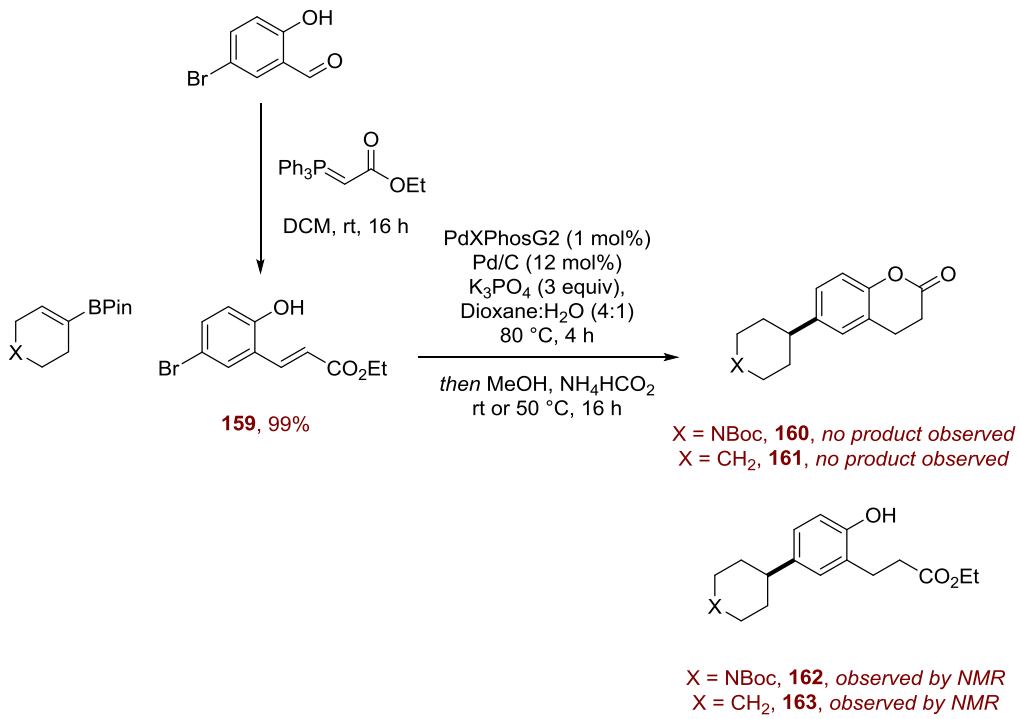
Scheme 84: Substrate scope of SM-TH reaction with respect to halide and boron component

Additional diversity could be achieved when using more functionalised aryl bromide precursors. For example, when ethyl 3-(5-bromo-2-nitrophenyl)acrylate (**156**) was used, an efficient *in situ* lactamisation took place, with three reductions and two bond-forming steps occurring in one pot, yielding **157** and **158** in excellent overall yield. The starting aryl bromide **156** was synthesised straightforwardly *via* a Wittig reaction using a stabilised phosphorus ylide.



Scheme 85: SM-TH reaction with *in situ* lactamisation to afford substituted dihydroquinolinones

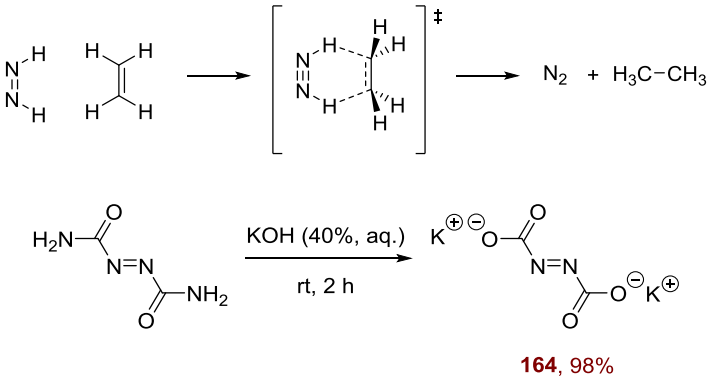
Similarly, this reaction protocol was attempted with ethyl 3-(5-bromo-2-hydroxyphenyl)acrylate (**159**) in an effort to synthesise a lactone. Good SM conversion and full hydrogenation was observed, however, no esterification occurred, even when the temperature of hydrogenation was increased.



Scheme 86: Attempts at SM-TH reaction with *in situ* lactonisation to afford substituted chromanones

3.6.3 Investigation into Olefin Reduction Using Diimides

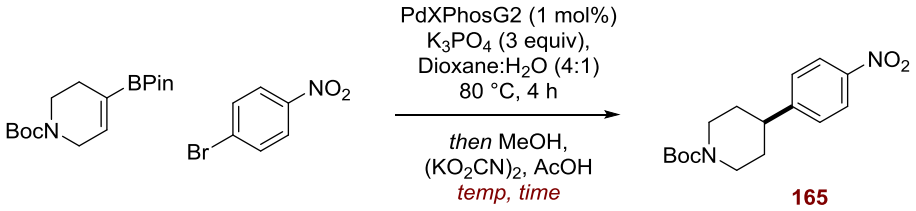
Following on from examination of alternative hydrogen sources, a diimide reduction was attempted, to achieve a selective olefin-reduction. Diimides are transient species which can be utilised in the addition of hydrogen across alkynes, allenes and alkenes. Mechanistically, the reaction involves the *syn* addition of dihydrogen across the carbon-carbon multiple bond, explained in Scheme 87. The diimide is usually synthesized *in situ* from the oxidation of hydrazine, or through decarboxylation of potassium azodicarboxylate (**164**). For this section of the study, potassium azodicarboxylate was chosen as the diimide source, and this was synthesised in excellent yields from the commercially available azodicarboxamide.



Scheme 87: Top, mechanism of reduction by diimide; bottom, synthesis of potassium azodicarboxylate

The SM reaction was performed as usual (in the absence of Pd/C), and a variety of conditions were examined using potassium azodicarboxylate in Table 35. Temperature, time and azodicarboxylate stoichiometry did not have an effect on the olefin reduction, but this may have been due to the inherent reactivity of the alkene in question.

Table 35: Investigation into olefin reduction of trisubstituted alkene using potassium azodicarboxylate



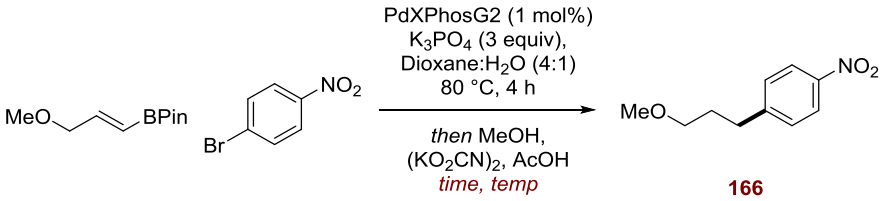
Entry	Time (h)	Temp	Eq. of $(KO_2CN)_2$	Hydrogenation (%)[a]
1	4	rt	20	0
2	16	rt	20	0
3	16	50 °C	20	0
4	16	rt	30	0

a) Determined by ^{1}H NMR

Generally, diimide reductions are most effective in terminal or disubstituted alkenes, and examples of trisubstituted alkene reductions are scarce. In light of this, the same reaction was tried using a disubstituted alkenyl BPin (Table 36). In this case, partial reduction was observed

however, counter-intuitively, increasing temperature and azodicarboxylate stoichiometry had a detrimental influence on olefin reduction. Increasing the time from 16 h to 40 h produced a marginal increase in the level of reduction but, based on these results, the investigation of this system was halted.

Table 36: Investigation into olefin reduction of disubstituted alkene using potassium azodicarboxylate



166

Entry	Time (h)	Temp	Eq. of $(KO_2CN)_2$	Hydrogenation (%)[a]
1	16	rt	20	62
2	16	50 °C	20	44
3	16	rt	30	59
4	40	rt	20	65

a) Determined by ^{1}H NMR

3.6.4 Application of Methodology towards the Synthesis of Biologically Active Targets

To conclude this section of the study, this modified procedure was applied to the syntheses of several biologically active compounds. 2-Amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) receptor potentiator, **167**, was firstly investigated.

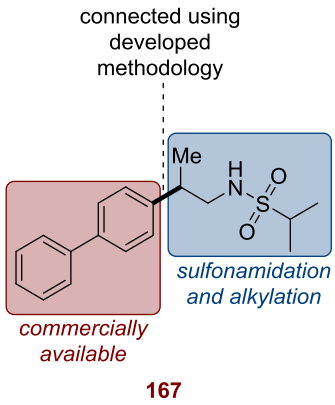
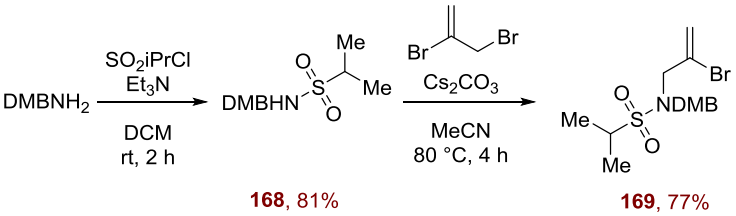


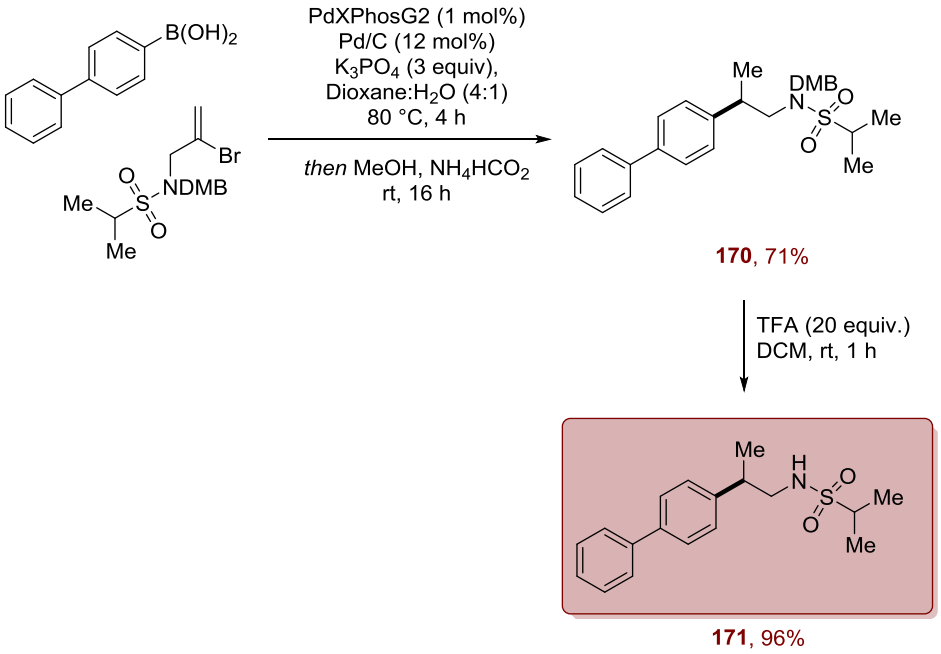
Figure 31: Target AMPA receptor potentiator with planned key disconnections highlighted

The right-hand fragment was formed *via* a sulfonamidation, followed by an S_N2 with 2,3-dibromopropene to give dimethoxybenzyl (DMB) protected vinyl bromide fragment **169**.



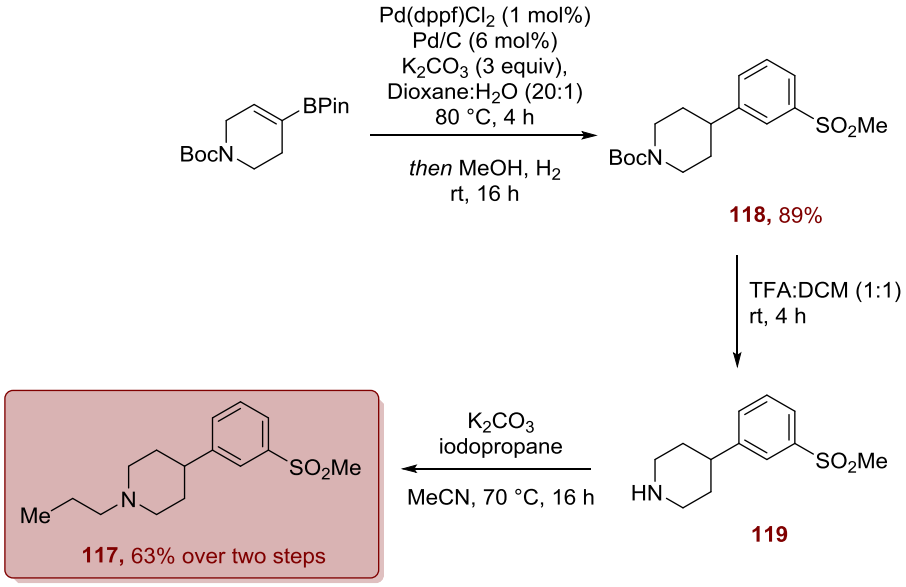
Scheme 88: Synthesis of DMB protected vinyl bromide fragment

169 was used in the reaction with biphenyl boronic acid, and a yield of 71% was achieved. Pleasingly, subsequent deprotection using TFA afforded the target AMPA modulator **171** in a 96% yield.



Scheme 89: Successful synthesis of AMPA modulator using developed methodology

Finally, the synthesis of pridopidine was re-examined using the modified conditions. The developed procedure was efficaciously applied to the first step in an excellent yield of 89%. Ensuing Boc deprotection and alkylation provided the target molecule successfully.

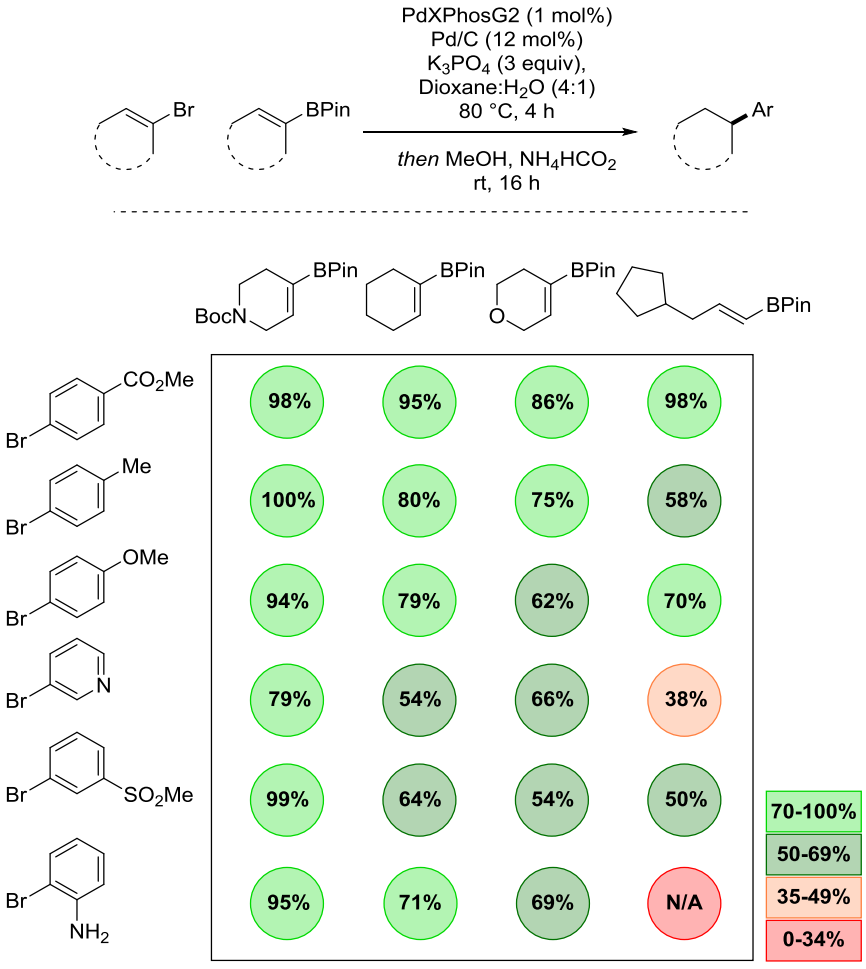


Scheme 90: Successful synthesis of pridopidine using developed methodology

3.6.5 Application of Methodology in an Array Synthesis Format

To illustrate the practicality of the process, the reaction's application within an array synthesis format was investigated. Array chemistry is used frequently within medicinal chemistry to make multiple analogues in parallel and can be a highly efficient method of compound synthesis.[197]

For this operation, the reactions were performed concurrently on a 0.125 mmol scale (Scheme 91). ^{1}H NMR was used to determine conversion using 1,4-dinitrobenzene as an internal standard. A selection of aryl bromides and vinyl BPins were chosen to provide molecules with a range of steric and electronic influences. This approach proved to be extremely successful – 23 of the 24 attempted molecules were synthesised, 22 of which occurred in a greater than 50% yield.

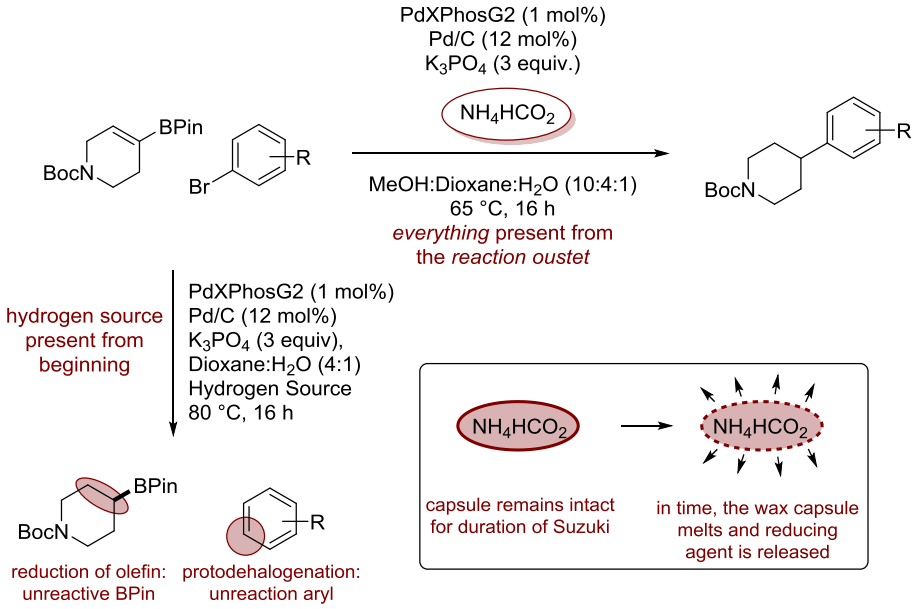


Scheme 91: Application of methodology to array synthesis format

As can be noted in the diagram above, a range of fragment and lead-like molecules have been synthesised in parallel from commercially available monomers. Due to the capricious nature of many other sp^2-sp^3 cross-coupling reactions, array application may not be possible using currently available methods, which emphasises the benefit of this developed process.

3.6.5 Development of a Wax Capsule Approach

A potential caveat with the methodology is the requirement to add the hydrogen source after a set period of time. Ideally, all reagents would be added to the reaction vessel at the beginning. Despite extensive experimentation, when a hydrogen source is present from the reaction outset, two main side reactions occur due to the hydrogenation out-competing the SM. The first is protodehalogenation of the aryl halide, and the second is reduction of the vinyl BPin to the corresponding alkyl BPin which, in most cases, undergoes subsequent protodeboronation. Each of these reactions renders the starting materials entirely unreactive.

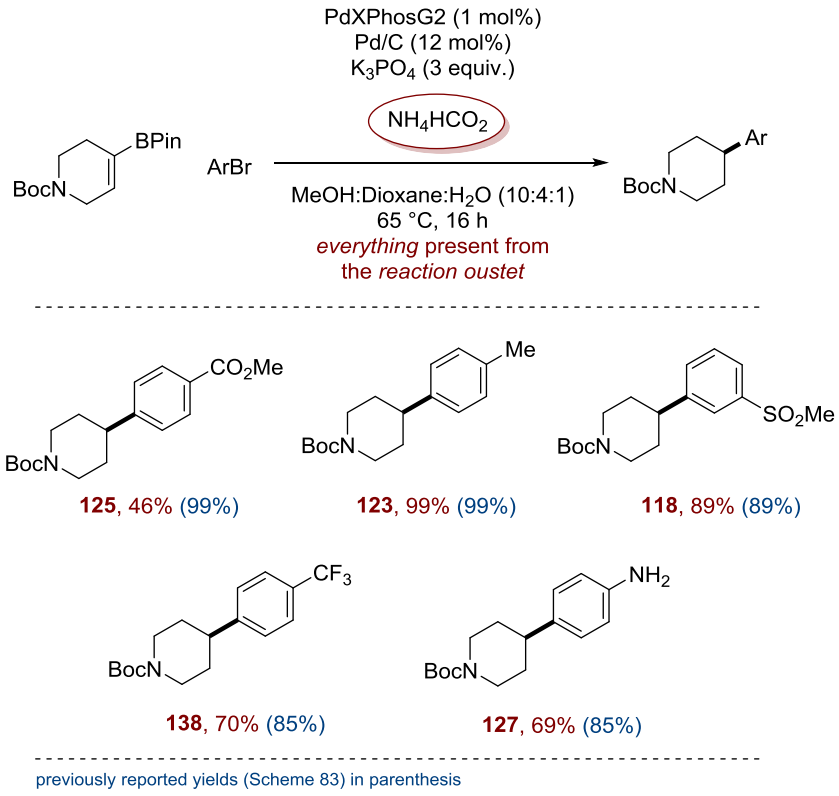


Scheme 92: Illustration of the wax capsule approach

To circumvent these problems, a degradable wax capsule was developed which allows for a controlled release of ammonium formate. A similar approach has been utilised by Buchwald and others, namely to facilitate easier handling of particularly air-sensitive compounds.[198] Firstly, the wax vessel had to be prepared from readily available materials. Paraffin wax with a reported melting point of >65 °C was chosen and melted with gentle heating in a conical flask. The molten wax was then added to an upturned Suba Seal using a glass pipette, and then an NMR tube was placed in the middle to create a hollow centre. After being held in place for

~1 minute, the NMR tube was removed from the solidified wax. The capsule was released from its mould, ammonium format was added, and then molten wax was dripped over the top to seal the vessel, which was then dipped in molten wax several times to ensure a full seal.

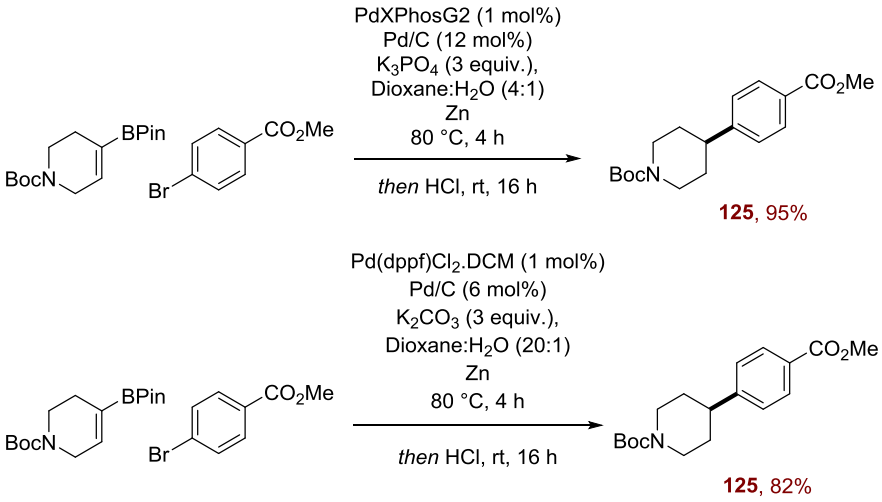
Investigation into the use of the capsule found that the choice of temperature was imperative. At 60 °C, the capsule did not melt, and no hydrogenation was observed. However, at 70 °C, the capsule melted almost immediately. When the reaction was performed at 65 °C, excellent coupling and full hydrogenation was observed. The established conditions were applied to a small range of substrates and all were found to be within ~10% of the previously obtained values. Ester **125** is an exception as partial hydrolysis to the corresponding acid was observed. Each entry was completed in duplicate with different capsules to ensure reproducibility.



Scheme 93: Application of encapsulated ammonium formate

3.6.6 Suzuki-Miyaura-Hydrogenation Using COware

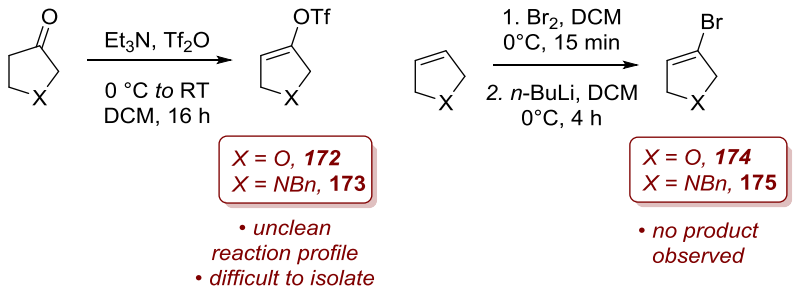
In the interest of practicality, the use of COware (*vide supra;* Scheme 72) to generate hydrogen was re-examined. Pleasingly, this method was found to be successful with either set of SM conditions and entirely avoids the handling of hydrogen gas.



Scheme 94: Successful implementation of COware apparatus using developed reaction conditions

3.7 Synthesis of 5-Membered Heterocyclic Vinyl Bromides

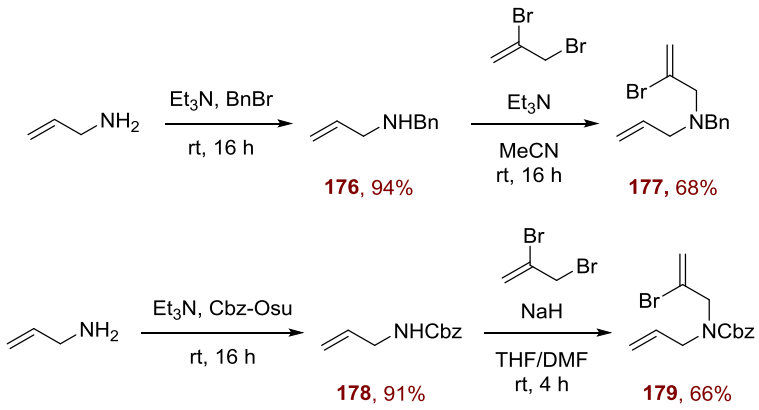
At this stage, 5-membered saturated heterocyclic systems had not been evaluated. Due to the lack of commercially available 5-membered heterocyclic vinyl halides or boron species, these required bespoke synthesis. Initially, the synthesis of vinyl triflates **172** and **173** was attempted from the corresponding ketone, however, this was unsuccessful, as was a dibromonation-elimination of a selection of saturated heterocyclic alkenes (to give **174** and **175**).



Scheme 95: Initial attempts at synthesis of vinyl triflates and bromides

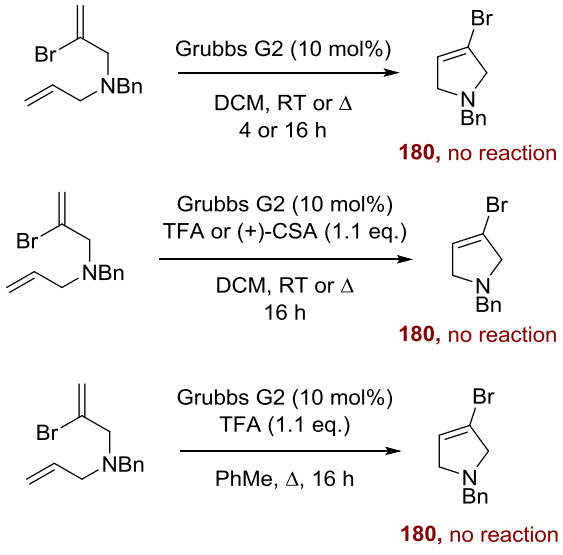
3.7.1 Initial Attempts at RCM towards 5-Membered Heterocyclic Vinyl Bromides

In light of these failed reactions, an RCM approach was examined. The intermediate bromo-dienes were synthesised in reasonable yields *via* the routes shown below:



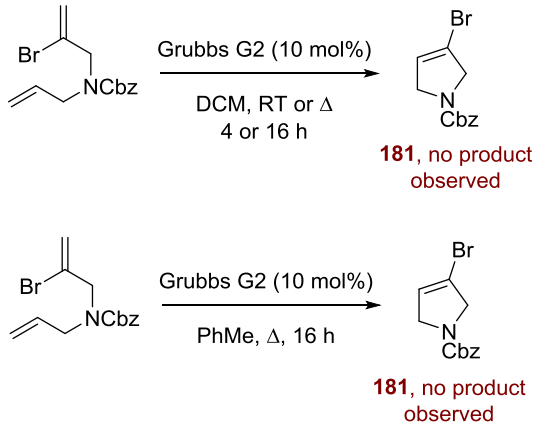
Scheme 96: Synthesis of bromo-diene starting materials for RCM investigation

With the dienes successfully prepared, the RCM step was explored, firstly with **177**. Using Grubbs G2 catalyst in 10 mol%, no reaction was observed. Basic amines are well known to inhibit RCM reactions by coordinating to the catalyst, which would explain the reaction outcome. To inhibit this interaction, various acids were added to protonate the amine, however this was not successful.



Scheme 97: RCM attempts with 177, with and without the addition of acid

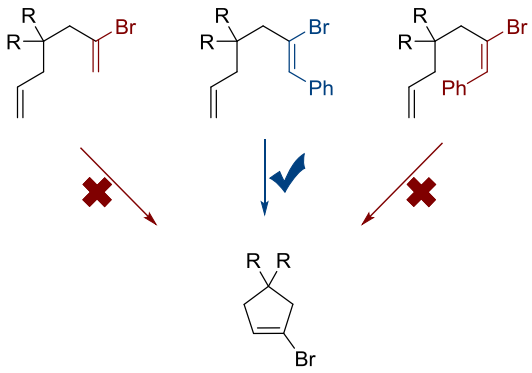
Diene **179** was next applied to the reaction, in the hope that the absence of a basic nitrogen may aid the metathesis. At room temperature, no conversion was observed, and when the reaction was heated, several byproducts were formed, with no product detected.



Scheme 98: Unsuccessful RCM attempts with 179

3.7.2 Second Approach of RCM towards 5-Membered Heterocyclic Vinyl Bromides

Examination of the relevant literature revealed that RCM reactions with vinyl halides fall into a rather unexplored area of chemistry. The small amount of work that has been performed on the subject has shown some RCM reactions with chlorides and fluorides, however very few examples of vinyl bromides have been reported. This has been attributed to a detrimental interaction between the bromine atom and the ruthenium catalyst. A recent publication by Dorta *et al*, however, suggests that the bromide moiety is not inherently detrimental, and only is problematic when it is forced into close proximity with the Ru centre.[199] Their hypothesis was that if the vinyl bromide could be shielded from the catalyst, degradation may not occur. This was achieved by introducing a sterically significant group on the terminal position of the olefin, in a *Z* geometry (when the alkene was *E*, no reaction was observed).



Scheme 99: Work of Dorta *et al.* on RCM of vinyl bromides and the importance of 'protecting' the catalyst

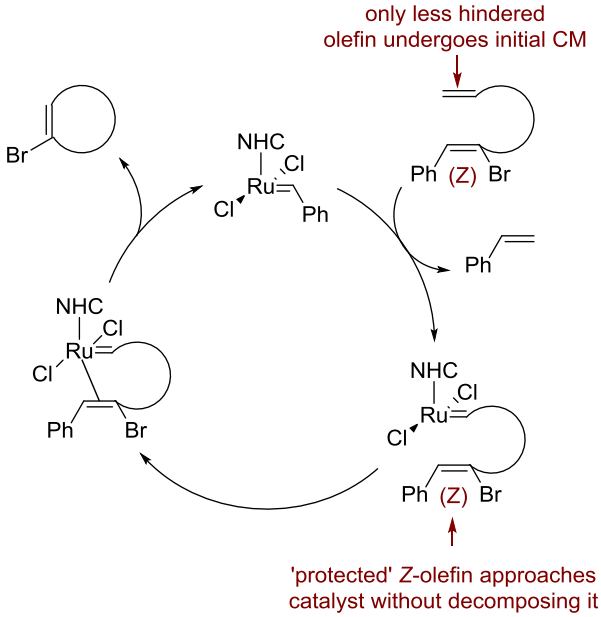
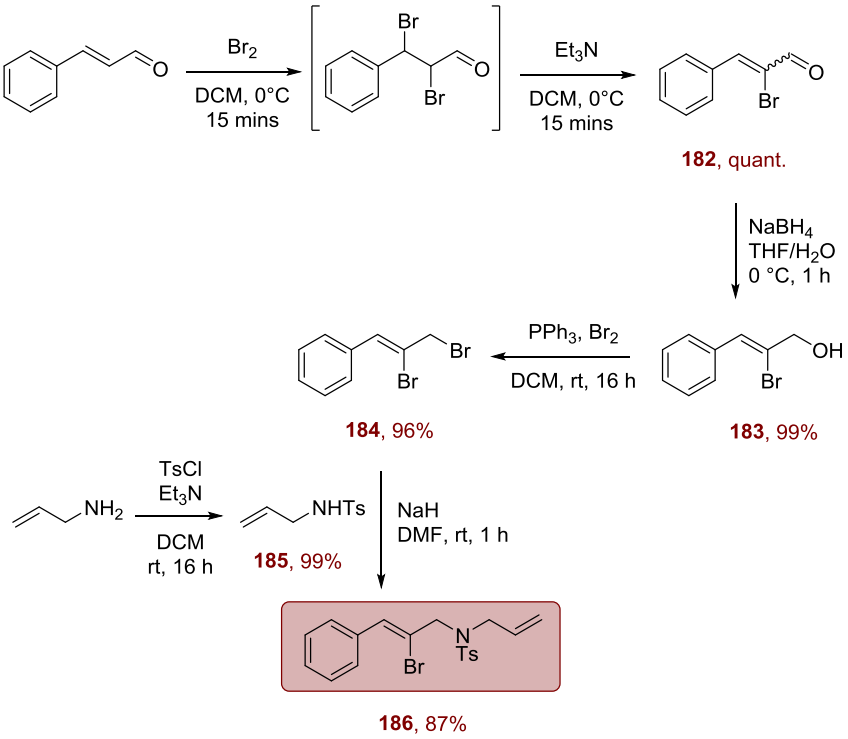


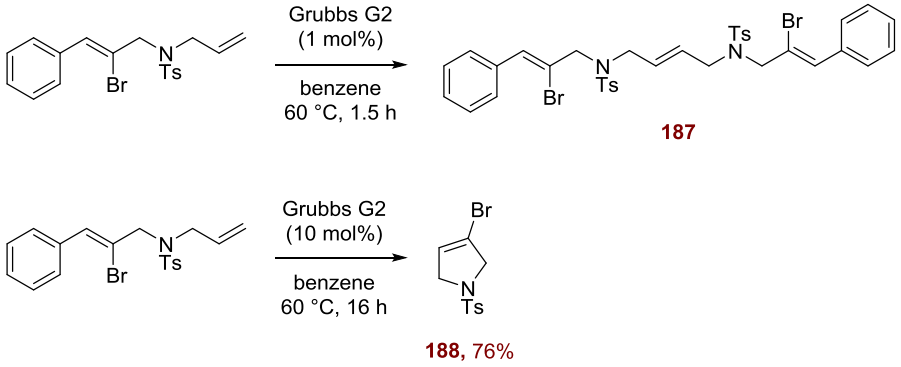
Figure 32: Proposed mechanism for RCM of vinyl bromides using 'protected' *Z*-olefin

Based on this work, phenyl substituted vinyl bromides were synthesised to improve the RCM step. Synthesis of these compounds began with bromonation of cinnamaldehyde with bromine, then treatment with triethylamine to afford vinyl bromide **182** in almost quantitative yields over the two steps (Scheme 100). The desired *Z* isomer was the minor isomer formed, however after being left for 3 days at room temperature, full isomerisation to the *Z* isomer occurred. Following this, the aldehyde was selectively reduced to the corresponding alcohol **183** using $NaBH_4$ in water and THF, which was subsequently converted to the primary bromide through an Appel reaction. Tosylation of allyl amine provided **185**, which was alkylated using bromide **184** to afford the diene which was subjected to RCM.



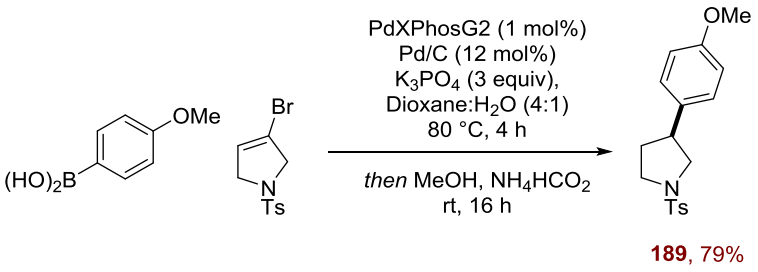
Scheme 100: Synthetic route towards bromo-diene from cinnamaldehyde

Using the conditions outlined by Dorta *et al*, the RCM of diene **186** was attempted, however, no ring-closed product was observed. The major component of the reaction was unreacted diene, with a small amount of cross-metathesised by-product isolated. Increasing the catalyst loading and halving the concentration allowed pyrroline product **188** to be isolated in a 76% yield. Cross-metathesised by-product **187**, starting diene and (*E*)-stilbene were also isolated or observed. (*E*)-stilbene was formed as a result of cross metathesis with two molecules of styrene, which is generated when RCM occurs.



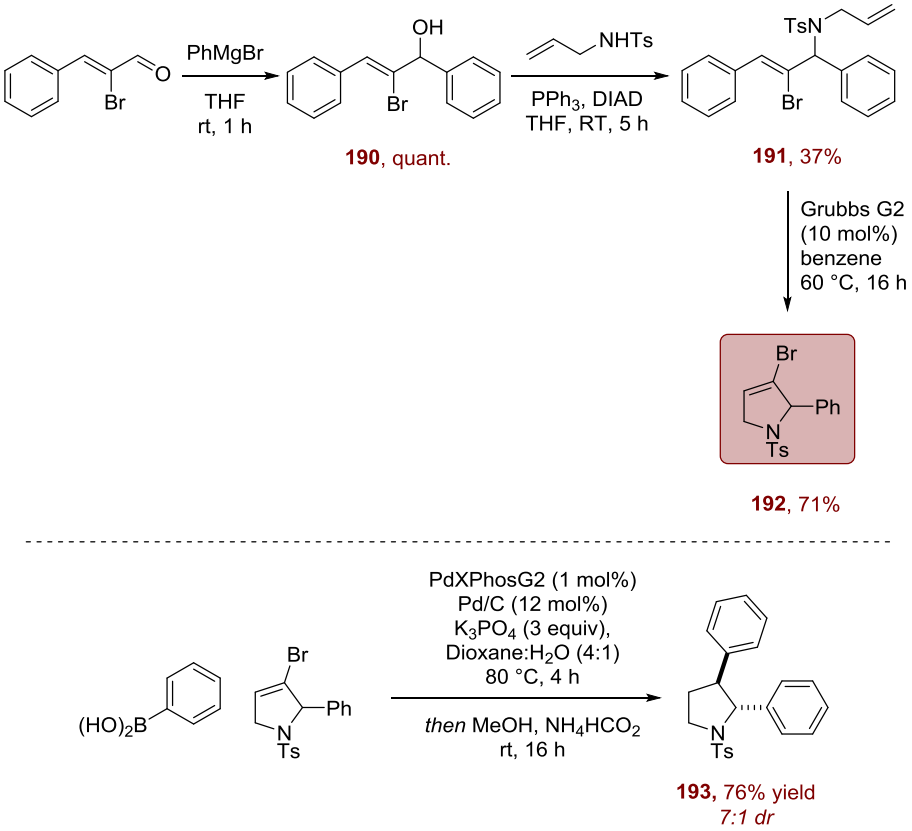
Scheme 101: RCM of 'protected' vinyl bromide using published conditions and modified conditions

Pleasingly, when **188** was used in the developed SM-TH manifold, the reaction proceeded in excellent yields to afford **189** (Scheme 102).



Scheme 102: Successful application of 188 to the SM-TH conditions

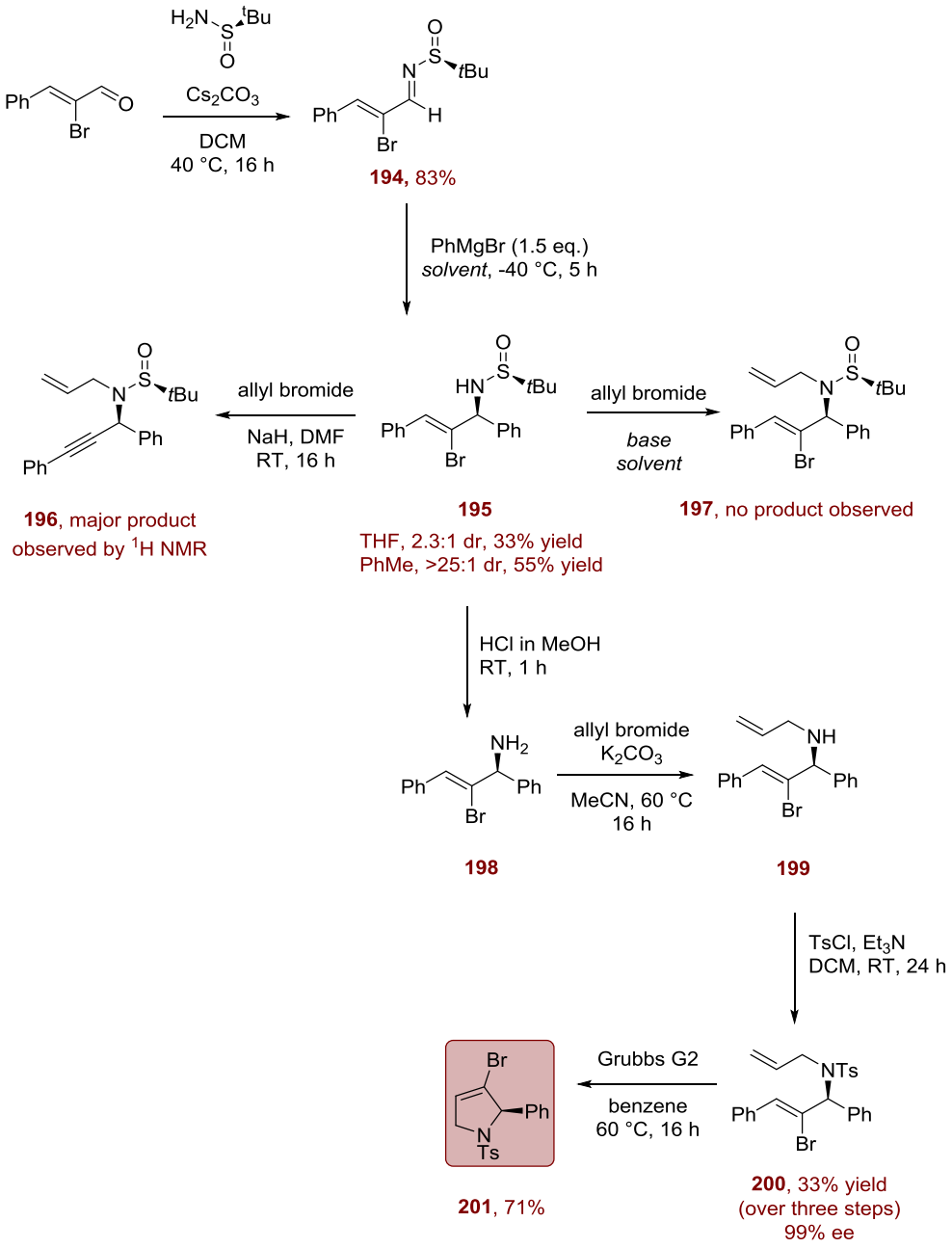
Following on from this, functionalised bromo-pyrrolines were synthesised to investigate the diasteroselectivity achieved in the SM-hydrogenation step (Scheme 103). Intermediate **182** was treated with phenyl magnesium bromide to afford secondary alcohol **190**, on which a Mitsunobu reaction was performed. The resulting diene was subjected to the RCM conditions to provide the desired phenyl substituted vinyl bromide. Application of this substrate to the SM-TH reaction provided **192** in excellent yield and a reasonable 7:1 dr.



Scheme 103: Route towards 2-substituted bromo-pyrroline scaffold and subsequent coupling using SM-TH conditions

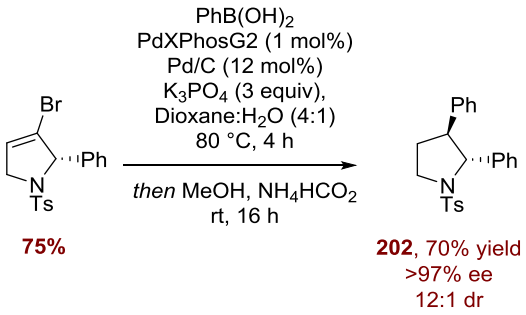
3.7.3 Synthesis of Enantioenriched Bromo-pyrroline

Having demonstrated the utility of substrates such as **192** (Scheme 103), a chiral variant was prepared using an Ellman auxiliary (Scheme 104). A condensation reaction with aldehyde **182** and (*R*)-Ellman sulfinamide, followed by a diastereoselective Grignard addition delivered chiral sulfinamide **195**. Interestingly, when THF was used as solvent, a dr of 2.3:1 was observed, however when THF was replaced by toluene, the dr increased to >25:1, and a single diastereomer could be isolated *via* normal phase column chromatography. Alkylation of **195** was more troublesome: when NaH was used, elimination of HBr occurred to afford the corresponding alkyne. Weaker bases and other solvents were examined; however, no product was detected in any case. Accordingly, the Ellman auxiliary was cleaved with acid, and the primary amine was alkylated and tosylated to provide the desired chiral diene **200** as a single enantiomer. RCM of **200** was successful, affording substituted bromo-pyrroline **201** in good yields.



Scheme 104: Asymmetric synthesis of 3-substituted bromo-pyrroline scaffold

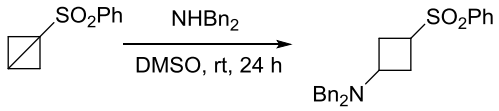
With chiral alkenyl bromide in hand, the key coupling step was attempted. Satisfyingly, an improved level of diastereoselectivity was achieved with an ee greater than 97%.



Scheme 105: Successful application of 201 to the SM-TH conditions

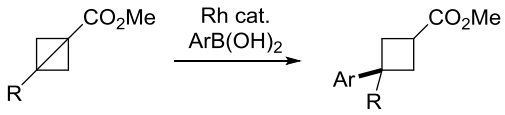
3.8 Rhodium-Catalysed Boronic Acid Conjugate Addition To Cyclobutane[1.1.0]bicycles

In keeping with the overarching aim of this research, a rhodium-catalysed conjugate-addition to cyclobutane[1.1.0]bicyclic systems was investigated. In recent years, interest in cyclobutane[1.1.0]bicyclic and cyclopentane[1.1.0]bicyclic systems has burgeoned. Firstly, research has shown them to be potential bio-isosteres for phenyl rings. Indeed, a direct substitution of a phenyl ring for bicyclo[1.1.1]pentane was found to positively impact the physicochemical properties of a lipoprotein-associated phospholipase A2 (LpPLA2) inhibitor.[200] Secondly, cyclobutane[1.1.0]bicyclic structures are susceptible towards attack from nucleophiles, to form substituted cyclobutanes. This was exemplified recently by Baran and coworkers, employing amines and thiols as nucleophiles (Scheme 106).[201]



Scheme 106: Example of Baran's recent strain release amination reaction

The proposed transformation, which is illustrated in Scheme 107, has the potential to form highly substituted cyclobutene fragments, molecules which are frequently found within biologically active compounds, as well as a range of natural products. Research surrounding these fragments has uncovered that the bond between C1 and C3 has a unique hybridisation and has been described as 'pseudo-olefinic', making the system akin to an α,β-unsaturated ester.[202,203] With this in mind, it was conjectured that an arylboronic acid/ester could perform conjugate addition to this 'pseudo-olefin' under rhodium-catalysed conditions.



Scheme 107: Proposed rhodium-catalysed conjugate-addition to substituted cyclobutane[1.1.0]bicycle

This work fits with ethos of the overall project by forming sp^2-sp^3 carbon bonds in systems which are prevalent in compounds with medicinal chemistry relevance. Substituted cyclobutanes are found in a range of approved drug molecules, including Sibutramine[204] and Butorphanol[205] (Figure 33).

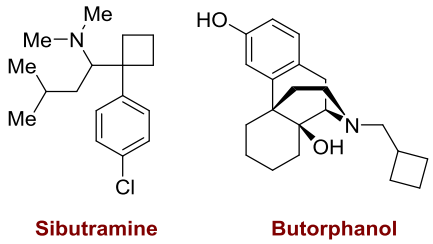
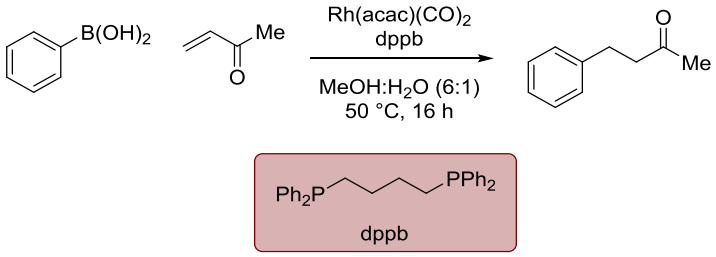


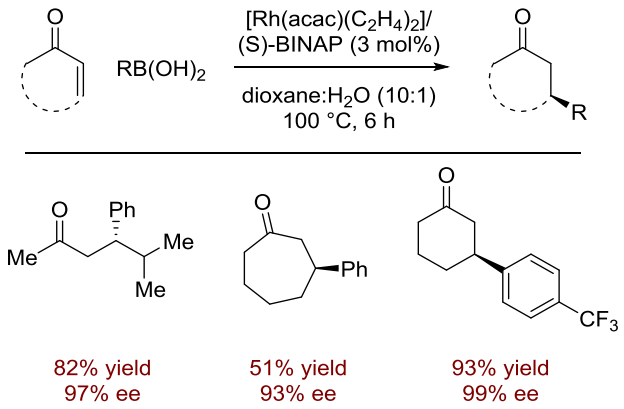
Figure 33: Structures of cyclobutane containing drugs, Sibutramine and Butorphanol

Rhodium-catalysed addition reactions using boronic acids have been known for 2 decades and have been utilised extensively in many areas of chemistry. The first example was published by Miyaura and co-workers in 1997, where they showed the addition of phenylboronic acid to methyl vinyl ketone.[206] A catalytic amount of neutral rhodium catalyst was used, along with phosphine ligand diphenylphosphinobutane (dppb) and the reaction was successful in a range of solvents.



Scheme 108: First example of rhodium-catalysed 1,4-addition by Miyaura and co-workers

Just 2 years later, Miyaura and Hayashi published an asymmetric variant of this reaction. Using (*S*)-BINAP with increased reaction temperatures, good yields and levels of enantioselectivity were achieved.[207]



Scheme 109: Selected examples from the first report of asymmetric rhodium-catalysed 1,4-addition by Miyaura and Hayashi

The mechanism of the reaction has been proposed to involve transmetallation of the boron-bearing aromatic group to rhodium, followed by insertion of the enone into the aryl-rhodium bond. Hydrolysis of this rhodium enolate gives the 1,4-addition product and a hydroxorhodium species. The generalised catalytic cycle is shown below in Figure 34.

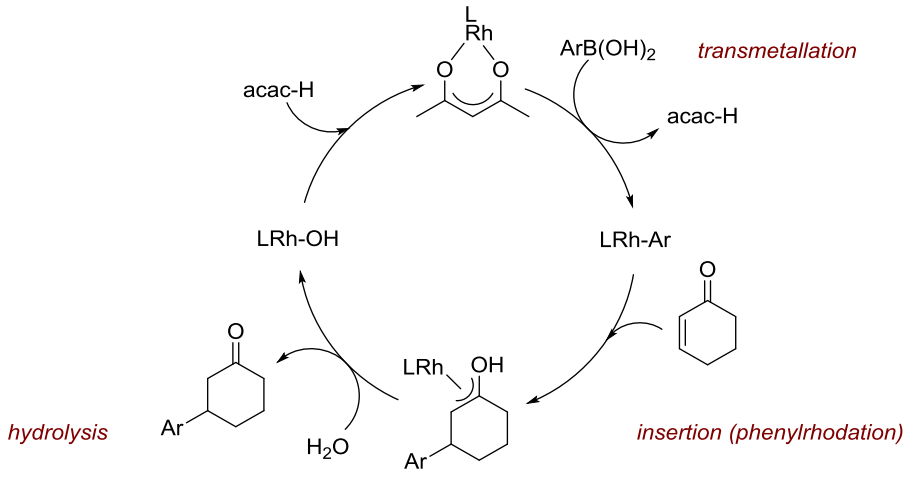
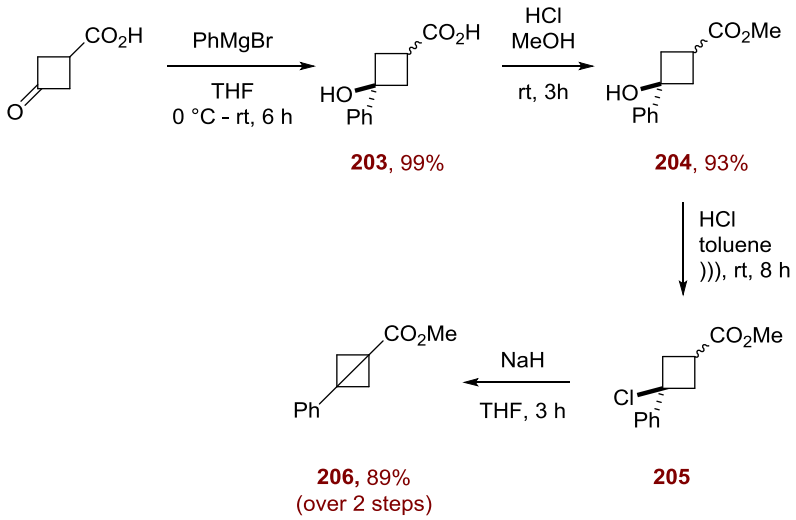


Figure 34: Generalised mechanism of Rh-catalysed conjugate addition using boronic acids

3.8.1 Synthesis of Ester Bearing Cyclobutane[1.1.0]bicycles

The synthesis of an analogue of **206** was reported in the literature, therefore this was the first target of interest to use as a starting material. With slight changes in the reported synthesis, **206** could be achieved *via* the route shown in Scheme 110. The synthesis began with a Grignard addition to a commercial cyclobutanone, followed by an esterification and chlorination. This intermediate was treated with base to initiate an intramolecular cyclisation to give **206**.

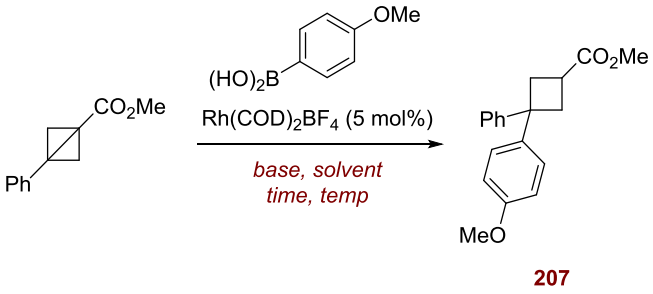


Scheme 110: Synthetic route to substituted cyclobutene[1.1.0]bicycle 206

3.8.2 Investigation into the Conjugate Addition Reactions to Ester Bearing Cyclobutane[1.1.0]bicycles

Preliminary studies into the addition reaction were performed using 4-methoxyboronic acid and $Rh(COD)_2BF_4$ as the catalyst.

Table 37: Initial investigative reactions into the addition of 4-methoxyboronic acid into 206

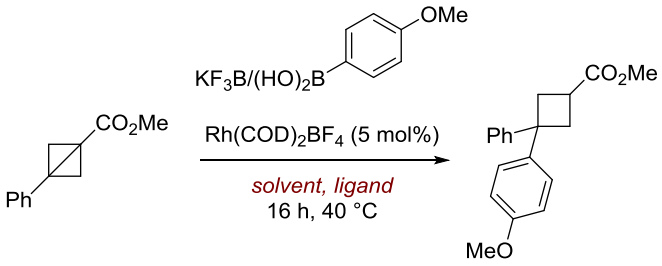


Entry	Temp	Time	Solvent	Base	Yield (%)
1	rt	16 h	Dioxane	-	0
2	rt	16 h	Dioxane:H_2O (10:1)	-	0
3	rt	16 h	Dioxane:H_2O (10:1)	KOH (3 eq.)	0
4	40 °C	16 h	Dioxane	-	0

5	40 °C	16 h	Dioxane:H_2O (10:1)	-	0
6	40 °C	16 h	Dioxane:H_2O (10:1)	KOH (3 eq.)	0
7	90 °C	16 h	Dioxane	-	0
8	90 °C	2 h	Dioxane	-	0
9	90 °C	8 h	Dioxane	-	0
10	90 °C	8 h	Dioxane:H_2O (10:1)	-	0
11	90 °C	8 h	Dioxane:H_2O (10:1)	KOH (3 eq.)	0

When the reaction was performed at room temperature, no consumption of starting material was observed. The inclusion of water as solvent, or the addition of base, did not change this outcome, and the reaction profile was identical at 40 °C. When the temperature was increased to 90 °C, after 16 h hours, the starting material had almost entirely degraded (Table 37, Entry 7). Accordingly, the reaction time was reduced to 2 h (Table 37, Entry 8), after which time, no consumption of starting material was again observed. After 8 hours at 90 °C, with or without base and water, no product was detected, with some degraded starting material being apparent.

Table 38: Investigation into the effect of boron species, solvent, water and ligand



207

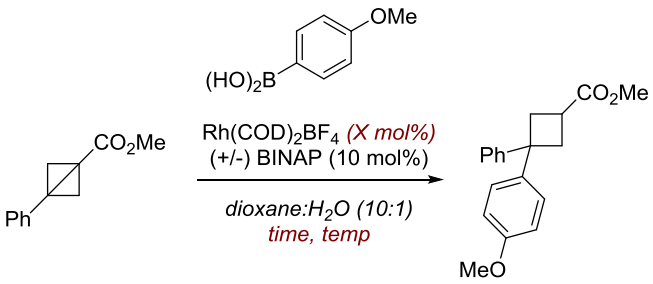
Entry	Boron	Solvent	Water	Ligand	Yield (%)
1	$B(OH)_2$	Dioxane	1 eq.	-	0
2	$B(OH)_2$	Dioxane	2 eq.	-	0

3	$B(OH)_2$	Dioxane	5 eq.	-	0
4	$B(OH)_2$	Dioxane	10 eq.	-	0
5	BF_3K	Dioxane	10:1	-	0
6	BF_3K	Dioxane	10:1	-	0
7	$B(OH)_2$	Dioxane	10:1	(+/-) BINAP	9
8	$B(OH)_2$	THF	10:1	-	0
9	BF_3K	THF	10:1	-	0
10	$B(OH)_2$	THF	10:1	-	0[a]
11	$B(OH)_2$	THF	10:1	(+/-) BINAP	0

a) Reaction performed at 70 °C

Following the initial studies, the stoichiometry of water was probed but this was found to have no positive effect. Changing the boron species from a boronic acid to BF_3K had no bearing on the reaction either. Pleasingly, however, it was found that the addition of phosphine ligand BINAP improved the reaction, and 9% of product was isolated. Changing the solvent from dioxane to THF did not improve the reaction, even at higher temperatures.

Table 39: Investigation into the effect of time, temperature and catalyst loading



207

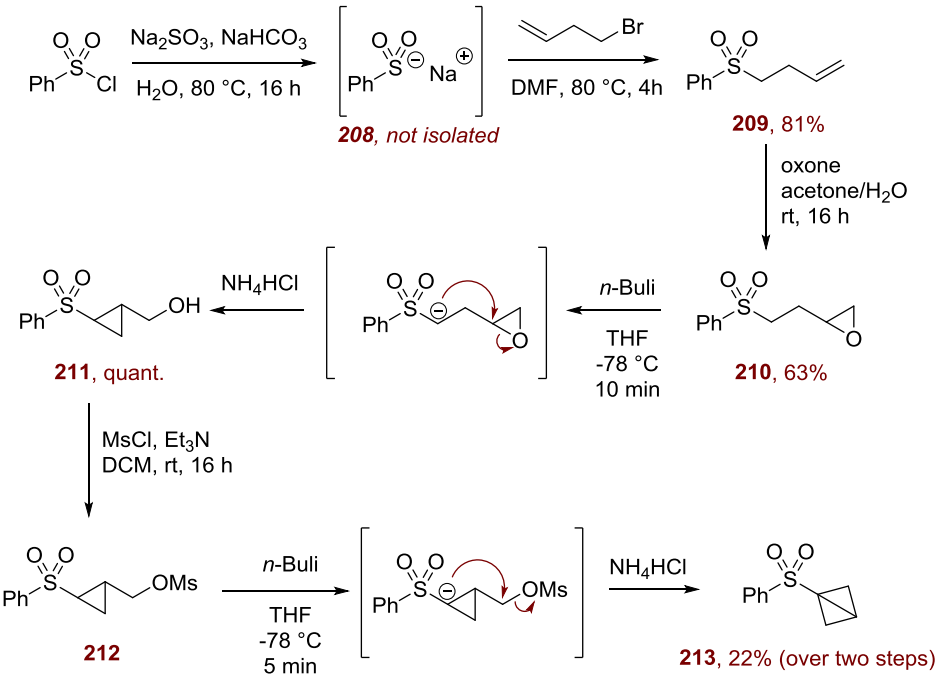
Entry	Time (h)	Temperature (°C)	Catalyst Loading (mol%)	Yield (%)
1	16	rt	5	0
2	48	40	5	10

3	72	40	5	7
4	16	100	5	0
5	48	100	5	0
6	16	40	10	10

When the reaction was performed at room temperature, no product was formed. Increasing the time or catalyst loading did not increase the yield by any appreciable amount. Unfortunately, increasing the temperature resulted in extensive degradation of starting material. Due to the instability of **206** at increased temperatures, and the low reactivity at decreased temperatures, an alternative starting material was investigated.

3.8.3 Synthesis of Sulfone Bearing Cyclobutane[1.1.0]bicycle

It has been previously reported that in the cyclobutene[1.1.0]bicyclic systems, sulfones provide the highest reactivity. Synthesis of these systems were based on recent work by Baran *et al.* (Scheme 111).[208] The route began with an alkylation of the sodium salt **208**. Epoxidation of the resultant alkene with oxone, followed by treatment with *n*-BuLi, afforded alcohol **211** which was subsequently mesylated. The addition of *n*-BuLi lead to the desired bicyclo[1.1.0]butane system *via* a cyclisation and displacement of $^{-}$OMs. The final step initially suffered from significant polymerisation, however decreasing the reactuib concentration avoided this side-reaction entirely. Although the yield in this step was relatively low, 60% of **212** could be consistently recovered and reapplied to the reaction conditions.

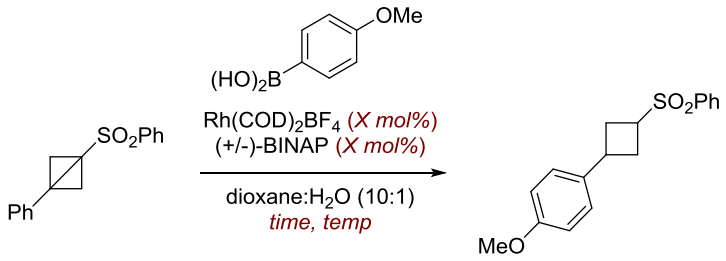


Scheme 111: Synthesis of cyclobutane[1.1.0]bicycle 213, with mechanism shown

3.8.4 Investigation into the Conjugate Addition Reactions to Sulfone Bearing Cyclobutane[1.1.0]bicycles

The most significant observation from the initial screening reactions was the increased stability of sulfone **213**. Even at 80 °C overnight, no degradation of starting material was observed. Unfortunately no conjugate addition product was isolated either (Table 40).

Table 40: Investigation into the effect of time, temperature and catalyst/ligand loading using sulfone 213



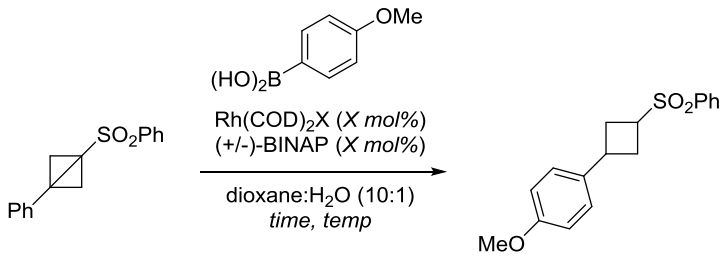
214

Entry	Time (h)	Temperature (°C)	Catalyst Loading (mol%)	Ligand Loading (mol%)	Yield (%)
1	8	rt	5	10	0
2	8	rt	10	20	0
3	16	rt	5	10	0
4	8	40	5	10	0
5	8	40	10	20	0
6	16	40	5	10	0
7	8	60	5	10	0
8	8	60	10	20	0
9	16	60	5	10	0
10	8	80	5	10	0
11	8	80	10	20	0
12	16	80	5	10	0

Having established the increased thermal stability of the sulfone cyclobutane[1.1.0]bicycle, the temperature was increased further, along with extended reaction times. Despite this, after

reaction at 100 °C for 36 hours, there was no sign of product (Table 41). Changing the counterion on the rhodium catalyst had no effect on the reaction, so the choice of substrate was re-examined.

Table 41: Investigation into the effect of time, temperature, counterion and catalyst/ligand loading



214

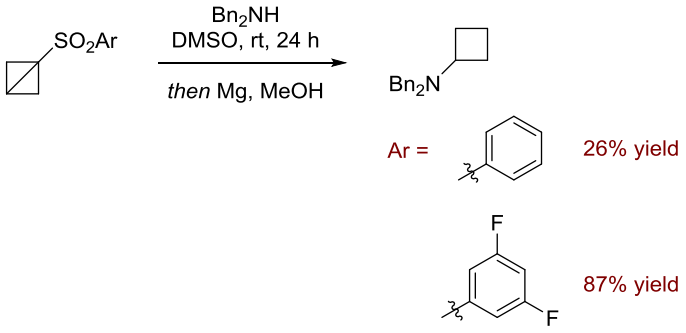
Entry	Time (h)	Temperature (°C)	Counterion & Catalyst Loading (mol%)	Ligand Loading (mol%)	Yield (%)
1	16	80	BF_4, 10	20	0
2	36	80	BF_4, 5	10	0
3	16	100	BF_4, 5	10	0
4	16	100	BF_4, 10	20	0
5	36	100	BF_4, 5	10	0
6	36	100	BF_4, 10	20	0, 0[a]
7	16	80	Cl, 10	20	0
8	36	80	Cl, 5	10	0
9	16	100	Cl, 5	10	0
10	16	100	Cl, 10	20	0
11	36	100	Cl, 5	10	0

12	36	100	Cl, 10	20	0, 0[a]

a) Reaction performed with 3 eq. of KOH

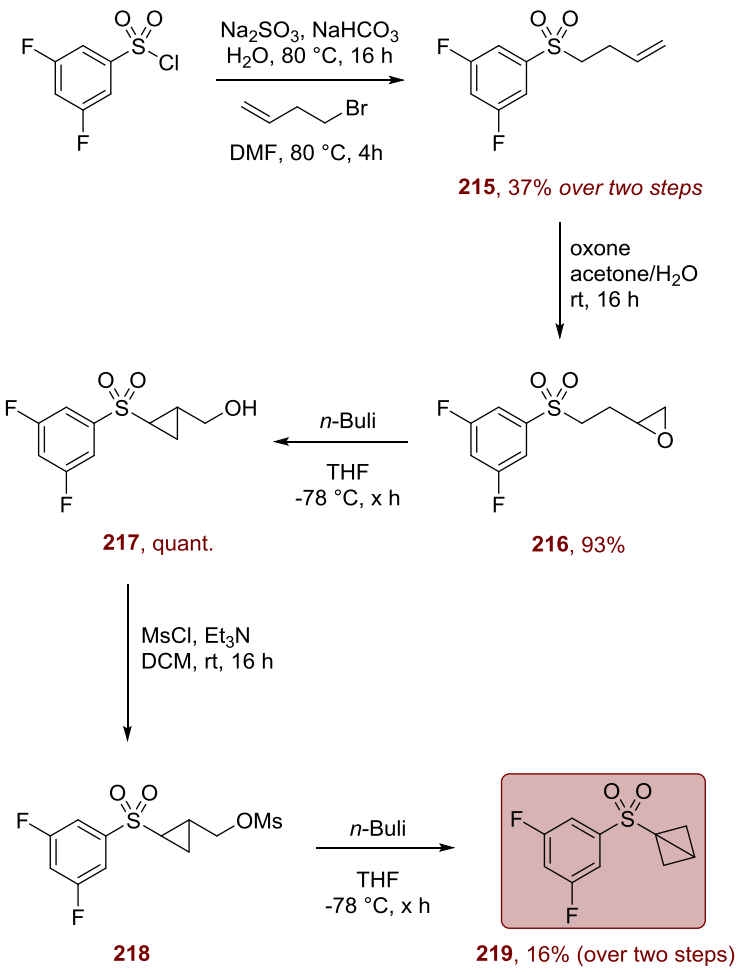
3.8.4 Synthesis of Fluorinated Sulfone Bearing Cyclobutane[1.1.0]bicycle

In their recent publication on strain release amination, Baran *et al.* showed that when the aromatic group was phenyl, the reaction occurred in a 26% yield. However, when the aromatic ring was made more electron deficient, i.e. when 3,5-difluoro **219** was used, the yield was increased to 87%.[208]



Scheme 112: Increased reactivity for electron poor aromatic rings, as shown by Baran *et al*[208]

Based on this, the 3,5-difluoro system was synthesised and utilised in a series of screening reactions. The synthetic route of **219** is shown below in Scheme 113. The final cyclisation occurred in poor yields, however, efforts to improve this (longer time, increased temperature, imcreased concentration) resulted in lower yields and polymerization. Again, ~70% of starting material could be recovered and re-subjected to the reaction conditions. Due to time constraints, these systems were not fully probed, and future work will involve investigation into reactions with these compounds.



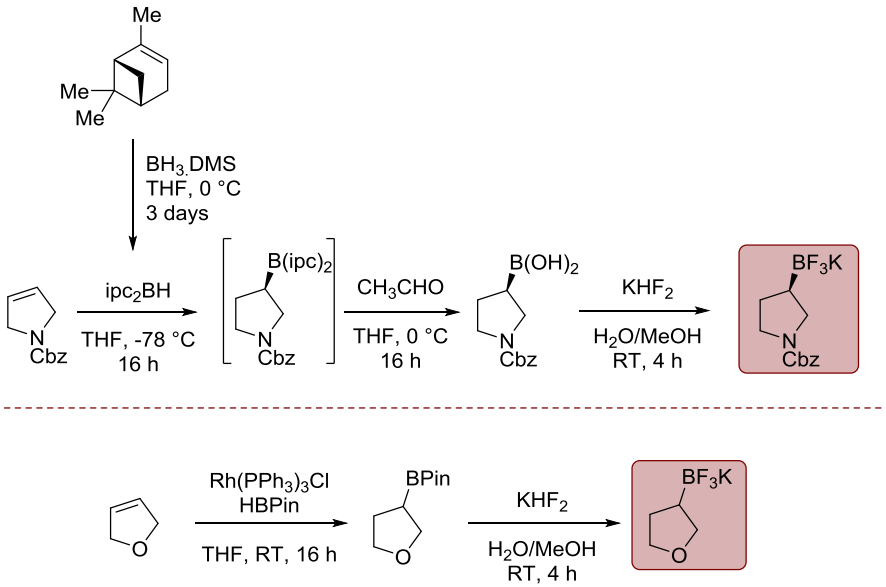
Scheme 113: Synthesis of cyclobutane[1.1.0]bicycle 219

3.8.5 Conclusions and Outlook

Despite only low yields of conjugate addition product being isolated, the reactions performed in this section allow for a proof-of-concept for the transformation. In the future, a focussed ligand screen may improve the reaction profile, in addition to investigation into other aspects of the reaction. In addition to what has been reported above, the acidity of the bridgehead proton of these systems was noted (this was later found to have been detailed in previous publications),[209,210] which could be exploited for a range of reactions (see Future Work). Judging by the observations during the investigations into reactions with cyclobutane[1.1.0]bicyclic systems, there clearly remains a vast depth of reaction potential. Due to time constraints, many of these transformations could not be investigated fully, however, further work may lead to further interesting and synthetically useful discoveries.

4. Conclusions

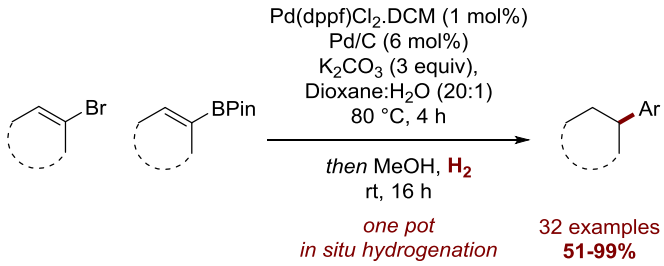
The initial aim of this research project was to facilitate a practical and useable synthesis of C-aryl linked saturated heterocyclic motifs. In order to achieve this, methods were developed towards the synthesis of racemic and chiral alkyl BF_3K salts.



Scheme 114: Synthesis of chiral and racemic alkyl BF_3K salts

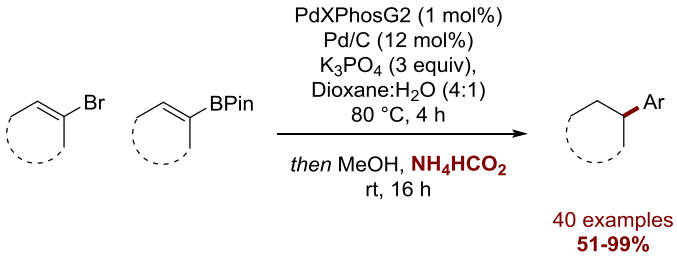
Despite extensive optimisation and reaction investigation, the cross-coupling stage was found to asymptote at around 20% and could not be increased past this point. Several interesting observations were made on this protocol, however, which could prove useful in future studies of the transformation.

The difficulties in this reaction, however, prompted the development of a new approach, which involved a formal sp^2-sp^3 cross-coupling *via* a single-pot SM-hydrogenation protocol. Examination of this procedure found that two catalysts were required, and the ratio of catalysts was critical to the success of the reaction. Having identified optimal conditions for the transformation, an extensive survey of tolerable substrates was performed. The results of this investigation were extremely encouraging, and the conditions were found to be highly applicable to a range of functionalities.



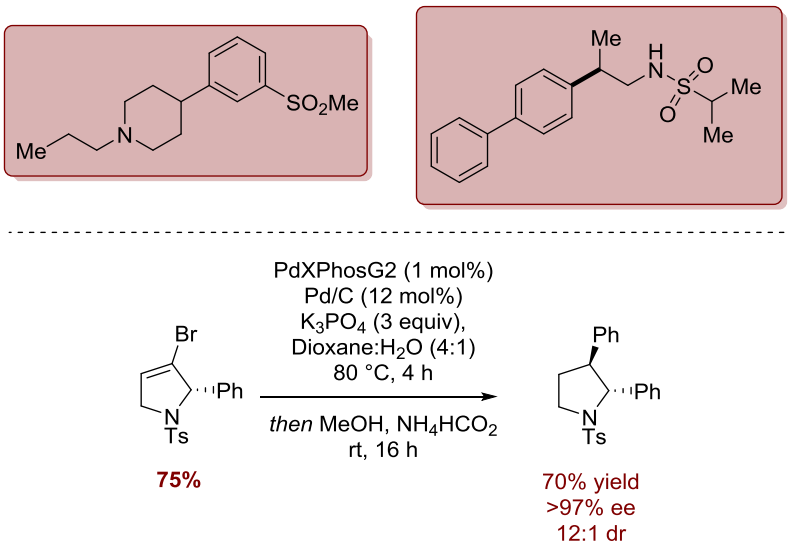
Scheme 115: Overview of developed SM-hydrogenation methodology

In a bid to improve the practicality of the protocol, a transfer-hydrogenation approach was investigated. An extensive ligand screen was performed, in addition to an examination of how each aspect of the reaction affected the hydrogenation. Again, the ratio of catalysts was key to the reductive step. The substrate scope was focussed on structures with biological relevance, synthesising a plethora of lead and fragment-like compounds with a high degree of saturation and chemical architectures commonly found in medicinal chemistry.



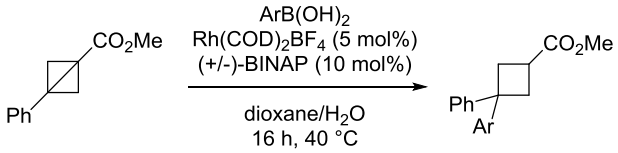
Scheme 116: Overview of developed SM-TH methodology

Moving on from this, the synthetic utility of the emerging process was tested further. A 6 x 4 array was performed with great success, as well as the successful synthesis of several biologically active compounds. New RCM methodology was adapted to allow the synthesis of chirally substituted and unsubstituted bromo-pyrrolines. These substrates worked well with the developed chemistry to synthesise substrates as single enantiomers and single diastereomers (Scheme 117).



Scheme 117: Top: Biologically active targets synthesised using the developed methodology; bottom: application of chirally substituted bromo-pyrrolines using developed methodology

Finally, exploratory reactions were performed to synthesise highly substituted cyclobutanes. Initial examination has allowed proof of concept and has identified interesting reactivity with these systems. Further work will undoubtedly improve the outcomes of the initial assessments.

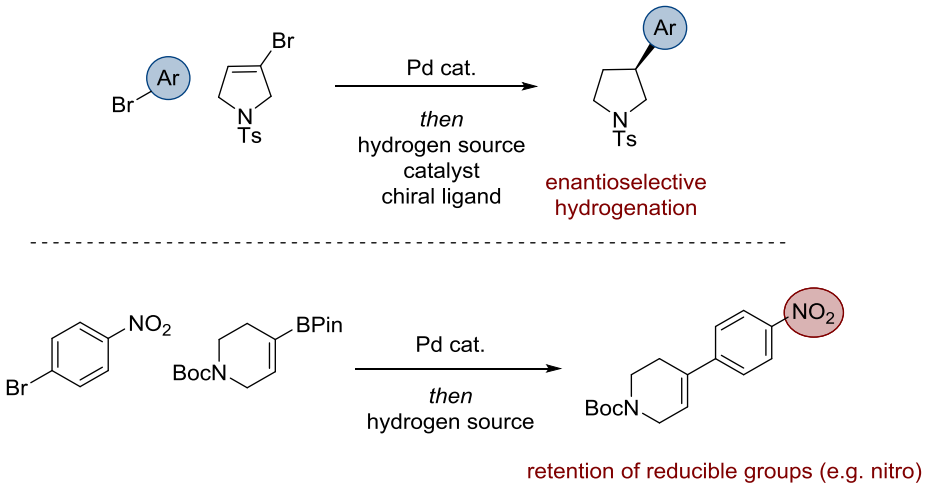


Scheme 118: General scheme of Rh-catalysed boronic acid conjugate addition

5. Future Work

Despite extensive optimisation, the cross-coupling protocol described within Section 3.4 was ultimately unsuccessful. Further endeavours with this transformation may be of use, with investigation focussing on the use of more developed precatalysts. The knowledge and understanding gained in this segment of work could be beneficial to future studies.

With regards to the SM-hydrogenation and transfer-hydrogenation procedures, future work will involve on the development of an asymmetric variant of the hydrogenation step. In addition to this, further hydrogen sources may be investigated in order to allow selective hydrogenation reactions for the instances of dual reduction (e.g. to retain nitro, Cbz, Bn groups etc.).



Scheme 119: Proposed enantioselective SM-hydrogenation reaction and olefin-selective hydrogenation

The synthesis of racemic and chiral cyclic vinyl bromides has been successful to this point, and further work will be performed to extend the scope of this procedure, to include different sized heterocycles, in addition to oxygen containing rings.

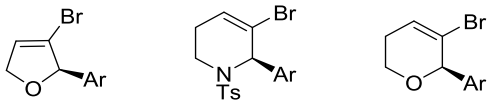
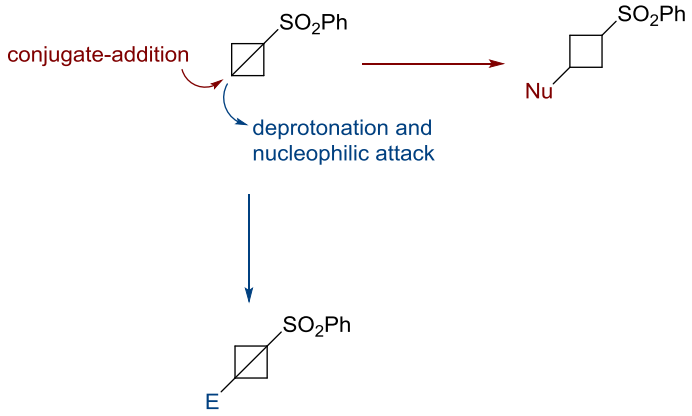


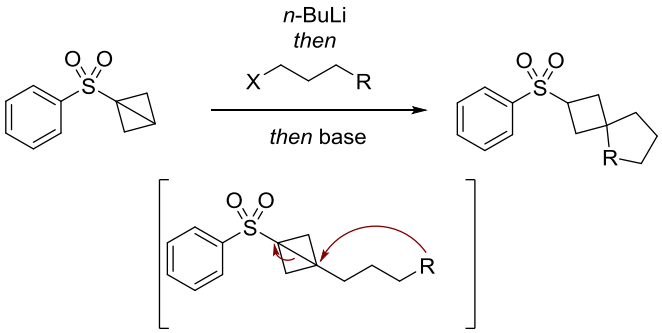
Figure 35: A selection of the proposed scope of cyclic vinyl bromides

In terms of the rhodium-catalysed conjugate addition reactions, additional probing of the reaction is required to develop the synthetic outcome. Extensive ligand screen may be required to improve the conversion, which will be performed in due course.

Finally, the unique reactivity of the bridgehead position of **213** could be exploited in an attempt to synthesise spirocyclic derivatives. Due to the acidity of the bridgehead proton, as well as the olefinic character, C3 of **213** can act as a nucleophile and electrophile – this phenomenon is illustrated in Scheme 120. The proposed spirocylclic synthesis is shown in Scheme 121.



Scheme 120: Illustration of electrophilic and nucleophilic nature of C3 of 213



Scheme 121: Proposed transformation towards spyrocycles of various sizes

6. Experimental

6.1 General Techniques

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[211] When purification was carried out *via* distillation, the relevant desiccants are indicated in brackets.

6.1.1 Purification of Solvents

i) Anhydrous THF was obtained from a PureSolv SPS-400-5 solvent purification system.
ii) 1,4-dioxane ($LiAlH_4$) and DMF ($MgSO_4$) were purified by vacuum distillation.
iii) Purified solvents were transferred to and stored in septum-sealed oven-dried flasks over previously activated 4 Å molecular sieves and purged with and stored under nitrogen.
iv) Acetone, dichloromethane, ethyl acetate, methanol, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

6.1.2 Experimental Details

i) All reactions were carried out using oven-dried glassware, which was evacuated and purged with N_2 before use, unless stated
ii) Purging refers to a vacuum/nitrogen-refilling procedure.
iii) Room temperature was generally *ca.* 20 °C.
iv) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.
v) Pd/C refers to 10% w/w purchased from Sigma Aldrich.
vi) For HPLC assays using caffeine standard, a 0.125 M solution of caffeine in MeCN was used. 2 mL of solution was added to each 0.25 mmol reaction, equating to a 1:4 ratio of caffeine:product.

6.1.3 Purification of Products

i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.
ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.
iii) Strong cation exchange chromatography was carried out using Silicycle SiliaPrepTM Propylsulfonic Acid (SCX-2) cartridges.

6.1.4 Analysis of Products

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained using an A2 Technologies ATR 32 machine.
ii) ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively, or on a Bruker AVANCE 400 spectrometer at 400 and 101 MHz respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.16 ppm (^{13}C), DMSO-d_6 referenced at 2.50 (^{1}H) and 39.52 ppm (^{13}C) and acetone-d_6 referenced at 2.05 (^{1}H) and 29.84 ppm (^{13}C).
iii) High-resolution mass spectra were obtained on a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Service Centre (NMSSC), Swansea.
iv) Chiral HPLC data was obtained on an Agilent 1260 Infinity HPLC using a Chiralpak IA column.
v) Optical rotations were measured at 589 nm using a Perkin Elmer 341 Polarimeter.

6.2 General Procedures

General Procedure A, racemic hydroboration of 2,5-dihydrofuran

To a solution of *catalyst* in dry THF (4 mL) was added 2,5-dihydrofuran (36 μL, 0.5 mmol, 1 eq.) and the reaction mixture was stirred for 5 minutes under nitrogen at room temperature. Borane reagent (0.5 mmol, 1 eq.). was then added dropwise and the reaction mixture was stirred at temperature under nitrogen for *time*, before being monitored by TLC or ^{1}H NMR. If successful, the reaction mixture was taken forward to purification using flash chromatography.

General Procedure B, enantioselective hydroboration of 2,5-dihydro-1*H*-pyrrole-1-carboxylate

To an oven dried round bottom flask was added (-)-α-pinene (155 µL, 1 mmol, 1 eq.) and dry THF (1 mL), and the mixture was cooled to -78 °C. BH_3.DMS (1M in THF, 2 mL, 2 mmol, 2 eq.) was added dropwise and the reaction was stirred at -78 °C for 8 h. At this point, the solvent was removed using a needle and the resulting white solid was washed with dry Et_2O before being dried under vacuum. The solid was dissolved in dry THF (2 mL) and cooled to *temp* before benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (152 mg, 0.75 mmol, 0.75 eq.) was added dropwise in dry THF (1 mL). The reaction was stirred at *temp* for X hours before being warmed to 0 °C. Following this, the reaction was warmed to 0 °C and NaOH (200 mg, 5 mmol, 5 eq.) and H_2O_2 (30% in water, 783 µL, 10 mmol, 10 eq.) were added and stirred for 2 h. The reaction was washed between Et_2O and sodium metabisulfite (aq.) solution. The organic layer was dried with Na_2SO_4 and applied directly to chrial HPLC to determine the enantiomeric excess.

General Procedure C, enantioselective hydroboration and subsequent boron speciation of 2,5-dihydro-1*H*-pyrrole-1-carboxylate

To an oven dried round bottom flask was added (-)-α-pinene (155 µL, 1 mmol, 1 eq.) and dry THF (1 mL), and the mixture was cooled to -78 °C. BH_3.DMS (1M in THF, 2 mL, 2 mmol, 2 eq.) was added dropwise and the reaction was stirred at -78 °C for 8 h. Following this, the mixture was allowed to sit undisturbed at 5 °C for 3 days. At this point, the solvent was removed using a needle and the resulting white solid was washed with dry Et_2O before being dried under vacuum. The solid was dissolved in dry THF and cooled to -78 °C before benzyl benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (152 mg, 0.75 mmol, 0.75 eq.) was added dropwise in dry THF (1 mL). The reaction was stirred at -78 °C for 8 hours before being warmed to 0 °C and aldehyde (2 eq.) in dry THF (1 mL) was added dropwise. After being stirred at room temperature for 8 hours, KHF_2 (4.5 M in water) (312 mg, 4 mmol, 4 eq.) and MeOH (1 mL) were added and the reaction was stirred at room temperature for 16 h. Following concentration *in vacuo*, the subsequent white solid was extracted three times with MeOH:Acetone (4:1, 10 mL) which was concentrated *in vacuo* until a precipitate began to appear. At this point, Et_2O was added to the mixture until the trifluoroborate salt precipitated from solution. Filtration afforded the title compound as a white solid.

General Procedure D, formation of sulfinimine using Ellman auxiliary

To a flask containing benzaldehyde (1 eq.) and DCM (0.2 M) was added (S)-*tert*-butanesulfinamide (1 eq.) and *additive*. The reaction was stirred at *temp* for 16 h before being

concentrated *in vacuo* and purified directly by flash chromatography (30% EtOAc/PE) to afford the title compound as a white amorphous solid.

General Procedure E, investigation into the hydroboration of 41

To an oven dried RBF was added *catalyst* and *solvent*, followed by 2-phenyl-2,5-dihydrofuran (37 mg, 0.25 mmol, 1 eq.). After stirring at room temperature for 5 minutes, pinacolborane (36 µL, 0.25 mmol, 1 eq.) was added dropwise. The reaction was stirred at *temp* for *time* before being analysed by TLC or ^{1}H NMR to determine conversion.

General Procedure F, sp^2-sp^3 SM reaction with 26

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), bromobenzene (26 µL, 0.25 mmol, 1 equiv), *catalyst*, and *base* (0.75 mmol, 3 eq.). The vial was capped and purged, then solvent and water were added. The reaction mixture was stirred at *temp* for *time* then was allowed to cool to room temperature and the vial was decapped. Caffeine solution was added to the reaction mixture, then a sample was taken up in a glass pipette, filtered through Celite and cotton wool and analysed by HPLC.

General Procedure G, sp^2-sp^3 SM reaction with 26 using varied aryl bromides

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) or trifluoro(tetrahydrofuran-3-yl)-borane, potassium salt (45 mg, 0.25 mmol, 1 eq.), aryl bromide (0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.), and K_3PO_4 (156 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then solvent and water were added. The reaction mixture was stirred at 80 ^{o}C for 16 h then was allowed to cool to room temperature and the vial was decapped. TLC and ^{1}H NMR was used to determine if product was present.

General Procedure H, optimisation of SM reaction using 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), bromobenzene (26 µL, 0.25 mmol, 1 equiv), *catalyst*, and *base* (0.75 mmol, 3 eq.). The vial was capped and purged, then *solvent* and *water* were added. The reaction mixture was stirred at 80 °C for 16 h then was allowed to cool to room temperature and the vial was decapped. Caffeine solution was added to the reaction mixture,

then a sample was taken up in a glass pipette, filtered through Celite and cotton wool and analysed by HPLC.

General Procedure I, initial substrate scope of SM-hydrogenation using Pd(dppf)Cl_2.DCM

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.) and K_2CO_3 (104 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h then MeOH (2 mL) was added. The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. Following this, the reaction was stirred vigorously for 16 h at room temperature under an atmosphere of hydrogen (using a balloon). The vial was then decapped, the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with ethyl acetate. The solvent was removed *in vacuo* and the crude ^{1}H NMR was performed before purification of product. If full hydrogenation was observed, the material was purified using flash chromatography.

General Procedure J, further optimisation of SM-hydrogenation

To an oven dried *reaction vessel* was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), aryl halide (0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.) and K_2CO_3 (104 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h then was allowed to cool to room temperature. The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. Following this, the reaction was stirred vigorously for *time* under an atmosphere of hydrogen (using a balloon) at *temperature*. The vial was then decapped, the reaction mixture was diluted with ethyl acetate, filtered through Celite and concentrated *in vacuo*. A ^{1}H NMR of the crude material was taken to determine the extent of hydrogenation.

General Procedure K, optimisation of SM-hydrogenation using a dual catalyst system

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-bromobenzotrifluoride (35 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM, Pd/C and K_2CO_3 (104 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then 1,4-dioxane (950 μL), water (50 μL) and *MeOH (X mL, when time = 0 h)* were

added. The reaction mixture was stirred at 80 °C for 4 h then was allowed to cool to room temperature and MeOH *MeOH (X mL, when time = 0 h)* was added. The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. Following this, the reaction was stirred vigorously for 16 h under an atmosphere of hydrogen (using a balloon) at room temperature. The vial was then decapped, the reaction mixture was diluted with ethyl acetate, filtered through Celite and concentrated *in vacuo*. A ^{1}H NMR of the crude material was taken to determine the extent of hydrogenation.

General Procedure L, substrate scope of SM-hydrogenation

To an oven dried 2-5 mL microwave vial was added boronic acid/ester, Pd(dppf)Cl_2.DCM (2 mg, 0.0025 mmol, 0.01 eq.), Pd/C (16 mg, 0.0175 mmol, 0.07 eq.), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and aryl halide. The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of MeOH (X mL). The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. After this, the reaction was stirred vigorously for 16 h at room temperature. The vial was de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solvent was removed *in vacuo* and the crude material was taken forward to purification.

General Procedure M, Implementation of Sajiki's chemistry on the one-pot procedure

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-benzyloxybromobenzene (66 mg, 0.25 mmol, 1 equiv) or benzyl *N*-(4-bromophenyl)carbamate (77 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.), Pd/C (16 mg, 0.0175 mmol, 0.06 eq), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and diphenyl sulfide (when time of Ph_2S addition = 0 h). The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h then was allowed to cool to room temperature and methanol (1 mL) and diphenyl sulfide (when time of Ph_2S addition = 4 h). was added. The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. Following this, the reaction was stirred vigorously for *time* under an atmosphere of hydrogen (using a balloon) at room temperature. The vial was then decapped, the reaction mixture was diluted with ethyl acetate, filtered through Celite and concentrated *in vacuo*. A ^{1}H NMR of the crude material was taken to determine the extent of hydrogenation.

General Procedure N, investigation into increasing hydrogen pressure for SM-hydrogenation

To an oven dried 2-5 mL microwave vial was added boronic acid/ester, $Pd(dppf)Cl_2$.DCM (2 mg, 0.0025 mmol, 0.01 eq.), Pd/C (16 mg, 0.0175 mmol, 0.07 eq.), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and aryl halide. The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of MeOH (X mL). When pressure = 1 bar: the vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes.

When pressure > 1 bar: the vial was decapped and placed in a hydrogen bomb, which was sealed and set to the correct pressure.

After this, the reaction was stirred vigorously for 16 h at room temperature and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solvent was removed *in vacuo* and the crude material was taken forward to purification.

General Procedure O, examination of ethanol as a co-solvent

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-bromobenzotrifluoride (35 μL, 0.25 mmol, 1 equiv), $Pd(dppf)Cl_2$.DCM (21 mg, 0.025 mmol, 0.1 eq.), *Pd/C* and K_2CO_3 (104 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h then was allowed to cool to room temperature and *ethanol (X mL)* was added. The vial was purged with hydrogen three times, before hydrogen was bubbled through the solvent for 5 minutes. Following this, the reaction was stirred vigorously for *time* under an atmosphere of hydrogen (using a balloon) at room temperature. The vial was then decapped, the reaction mixture was diluted with ethyl acetate, filtered through Celite and concentrated *in vacuo*. A ^1H NMR of the crude material was taken to determine the extent of hydrogenation and, if necessary, taken forward for further purification.

General Procedure P, Initial investigation into TH reaction using triethylsilane

To an oven dried 2-5 mL microwave vial was added 4-phenyl-3,6-dihydro-2*H*-pyran (40 mg, 0.25 mmol, 1 eq.) and *catalyst.* The vial was capped and purged, then *solvent (1 mL)* and triethylsilane (120 μL, 0.25 mmol, 3 eq.). The reaction was stirred at room temperature for *time,* then the reaction was diluted with ethyl acetate and filtered through Celite. Following

concentration *in vacuo*, a ^{1}H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure Q, application of TH conditions to the one-pot procedure

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), bromobenzene (26 μL, 0.25 mmol, 1 equiv.), Pd(dppf)Cl_2.DCM (2 mg, 0.002 5 mmol, 0.01 eq.), Pd/C (16 mg, 0.0175 mmol, 0.07 eq.), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and aryl halide. The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for. After this, *additive* (1 mL) and triethylsilane (120 μL, 0.25 mmol, 3 eq.) were added and the reaction was stirred vigorously for *time* at room temperature. The vial was de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solvent was removed *in vacuo* and a ^{1}H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure R, investigation into the effect of base and water on the TH aspect of the reaction

To an oven dried 2-5 mL microwave vial was added 4-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran (57 mg, 0.25 mmol, 1 eq.), Pd/C (16 mg, 0.015 mmol, 0.06 eq.) and *additive (for bases: 0.75 mmol, 3 eq.).* The vial was capped and purged, and then *solvent (1 mL)* and triethylsilane (120 μL, 0.25 mmol, 3 eq.) were added. The reaction was stirred at room temperature for 30 minutes, then the reaction was diluted with ethyl acetate and filtered through Celite. Following concentration *in vacuo*, a ^{1}H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure S, investigation into the effect of ligand additives on the TH reaction

To an oven dried 2-5 mL microwave vial was added 4-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2*H*-pyran (57 mg, 0.25 mmol, 1 eq.), Pd/C (16 mg, 0.015 mmol, 0.06 eq.) and *ligand.*. The vial was capped and purged, and then dioxane (1 mL) and triethylsilane (120 μL, 0.25 mmol, 3 eq.) were added. The reaction was stirred at room temperature for 30 minutes, and then the reaction was diluted with ethyl acetate and filtered through Celite. Following concentration *in vacuo*, a ^{1}H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure T, application of ligand results in to the two-step, one-pot process

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-bromobenzotrifluoride (35 μL, 0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol, 0.01 eq.), *ligand, Pd/C*, K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and aryl halide. The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of MeOH (1 mL) and triethylsilane (120 μL, 0.25 mmol, 3 eq.). The reaction was stirred vigorously for 16 h at room temperature, de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. Following concentration *in vacuo*, a ^1H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure U, application of precatalysts in to the two-step, one-pot process

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-bromobenzotrifluoride (35 μL, 0.25 mmol, 1 equiv.), Pd(OAc)2 (0.6 mg, 0.0025 mmol, 0.01 eq.), *precatalyst (X mg, 0.0025 mmol, 0.01 eq.), Pd/C (see table for amount),* K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) and aryl halide. The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of MeOH (1 mL) and triethylsilane (120 μL, 0.25 mmol, 3 eq.). The reaction was stirred vigorously for 16 h at room temperature, decapped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. Following concentration *in vacuo*, a ^1H NMR was taken on the crude material to determine the extent of hydrogenation.

General Procedure V, Further optimisation of SM-TH conditions

To an oven dried 2-5 mL microwave vial was added 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), methyl-4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.), catalyst, Pd/C, Base (0.75 mmol, 3 equiv.). The vial was capped and purged, then 1,4-dioxane and water (total volume = 1 mL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of NH_4HCO_2 in MeOH (1.25 M) (158 mg NH_4HCO_2 in 2 mL MeOH, 10 eq. 2.5 mmol). After this, the reaction was stirred for 16 h at room temperature. The vial was de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solvent was removed *in vacuo* and the crude material was taken forward to purification.

General Procedure W, substrate scope of SM-transfer-hydrogenation

To an oven dried 2-5 mL microwave vial was added boronic ester/acid (0.25 mmol, 1 equiv.), PdXPhosG2 (2 mg, 0.0025 mmol, 0.01 equiv.), 10% Pd/C (32 mg, 0.04 mmol, 0.12 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.) and aryl halide (0.25 mmol, 1 equiv.). The vial was capped and purged, then 1,4-dioxane (800 µL) and water (200 µL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of NH_4HCO_2 in MeOH (1.25 M) (158 mg NH_4HCO_2 in 2 mL MeOH, 10 eq. 2.5 mmol). After this, the reaction was stirred for 16 h at room temperature. The vial was de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solvent was removed *in vacuo* and the crude material was taken forward to purification.

General Procedure X, investigation into olefin reduction using potassium azodicarboxylate

To an oven dried 2-5 mL microwave vial was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), PdXPhosG2 (2 mg, 0.0025 mmol, 0.01 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.) and 4-bromonitrobenzene (50 mg, 0.25 mmol, 1 equiv.). The vial was capped and purged, then 1,4-dioxane (800 µL) and water (200 µL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of $(KO_2CN)_2$ and AcOH (571 µL, 10 mmol, 40 eq.). The reaction was stirred for *time* at *temp* before being washed between water and ethyl acetate and dried with Na_2SO_4. ^{1}H NMR was used to determine the extent of hydrogenation.

General Procedure Y, investigation into olefin reduction using potassium azodicarboxylate

To an oven dried 2-5 mL microwave vial was added (*E*)-2-(3-methoxyprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 mg, 0.25 mmol, 1 equiv.), PdXPhosG2 (2 mg, 0.0025 mmol, 0.01 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.) and 4-bromonitrobenzene (50 mg, 0.25 mmol, 1 equiv.). The vial was capped and purged, then 1,4-dioxane (800 µL) and water (200 µL) were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of $(KO_2CN)_2$ and AcOH (571 µL, 10 mmol, 40 eq.). The reaction was stirred for *time* at *temp* before being washed between water and ethyl acetate and dried with Na_2SO_4. ^{1}H NMR was used to determine the extent of hydrogenation.

General Procedure Z, array synthesis application

To a test tube was added Bpin (0.125 mmol, 1 eq.), PdXPhosG2 (1 mg, 0.00125 mmol, 0.01 eq.), Pd/C (16 mg, 0.015 mmol, 0.12 eq.), K_3PO_4 (79 mg, 0.375 mmol, 3 eq.) and aryl halide (0.125 mmol, 1 eq.). The test tube was sealed with a suba seal, purged with nitrogen, then 1,4-dioxane and water were added. The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of NH_4HCO_2 in MeOH (1.25 M) (79 mg NH_4HCO_2 in 1 mL MeOH, 10 eq. 1.25 mmol). Following this, the reaction was stirred for 16 h at room temperature before 1,4-dinitrobenzene (10.5 mg in MeCN) was added and the reaction was filtered through Celite. Concentration *in vacuo* afforded the crude material, on which a ^{1}H NMR was performed. Conversion was determined by using 1,4-dinitrobenzene as an internal standard.

General Procedure AA, application of wax capsule chemistry

To a boiling tube was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), PdXPhosG2 (2 mg, 0.0025 mmol, 0.01 equiv.), 10% Pd/C (32 mg, 0.04 mmol, 0.12 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), aryl halide (0.25 mmol, 1 eq.) and a wax capsule containing ammonium formate (158 mg, 2.5 mmol, 10 equiv.). The tube was capped with a Suba Seal, purged then charged with 1,4-dioxane (800 µL), water (200 µL) and MeOH (2 mL). The reaction was stirred at 65 °C for 16 h, filtered through Celite then concentrated *in vacuo* before being taken forward to purification.

Preparation of capsule: ≥65% paraffin wax was heated in a conical flask until fully melted and transferred to an unturned Suba Seal using a glass pipette. An NMR tube was placed in the molten wax to create a hollow centre and was held in position for ~1 minute until the wax had solidified. Following this, the Suba Seal was folded over to free the wax capsule, to which ammonium formate was added. Molten wax was dripped over the open capsule to fully encapsulate the ammonium formate, and then the full capsule was dipped in a conical flask of molten wax twice to ensure a full seal, then allowed to cool to room temperature.

General Procedure BB, RCM attempts to synthesis vinyl bromide with benzyl protected amine

To an oven-dried flask containing *N*-allyl-*N*-benzyl-2-bromoprop-2-en-1-amine (67 mg, 0.25 mmol, 1 eq.) and dry solvent (25 mL) was added Grubbs' G2 catalyst (20 mg, 0.025 mmol, 0.1 eq.) and *acid (0.38 mmol, 1.5 eq.)*. The reaction was stirred for time at temperature then filtered through a pad of silica and concentrated *in vacuo*. The reaction was analysed by ^{1}H

NMR and/or TLC to determine conversion to product.

General Procedure CC, RCM attempts to synthesis vinyl bromide with Cbz protected amine

To an oven-dried flask containing benzyl allyl(2-bromoallyl)carbamate (78 mg, 0.25 mmol, 1 eq.) and dry solvent (25 mL) was added *Grubbs' G2 catalyst*. The reaction was stirred for *time* at *temperature* then filtered through a pad of silica and concentrated *in vacuo*. The reaction was analysed by ^{1}H NMR and/or TLC to determine conversion to product.

General Procedure DD, initial investigative reactions into the addition of 4-methoxyboronic acid into 206

To an oven dried 2-5 mL microwave vial was added methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (47 mg, 0.25 mmol, 1 eq.), 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 eq.), $Rh(COD)_2BF_4$ (5 mg, 0.0125 mmol, 0.05 eq.) and *KOH (42 mg, 0.75 mmol, 3 eq.) where appropriate*. The vial was capped and purged, and then 1,4-dioxane and water (total volume of 1 mL) was added. The reaction was stirred at *temperature* for *time* before being washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography was performed to determine if any product was present.

General Procedure EE, investigation into the effect of boron species, solvent, water and ligand

To an oven dried 2-5 mL microwave vial was added methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (47 mg, 0.25 mmol, 1 eq.), 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 eq.) or trifluoro(4-methoxyphenyl)-borane, potassium salt (54 mg, 0.25 mmol, 1 eq.), $Rh(COD)_2BF_4$ (5 mg, 0.0125 mmol, 0.05 eq.) and (+/-)-*BINAP (16 mg, 0.025 mmol, 0.1 eq.).* The vial was capped and purged, and then *solvent* and water (total volume of 1 mL) was added. The reaction was stirred at 40 ^{o}C (except Entry 10, which was performed at 70 ^{o}C) for 16 h before being washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography was performed to determine if any product was present.

General Procedure FF, Investigation into the effect of time, temperature and catalyst loading

To an oven dried 2-5 mL microwave vial was added methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (47 mg, 0.25 mmol, 1 eq.), 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 eq.), $Rh(COD)_2BF_4$. The vial was capped and purged, and then 1,4-dioxane and water (total

volume of 1 mL) was added. The reaction was stirred at *temperature* for *time* before being washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography was performed to determine if any product was present.

General Procedure GG, investigation into the effect of time, temperature and catalyst/ligand loading using sulfone 213

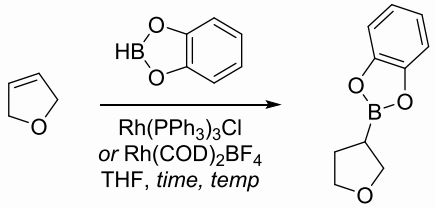
To an oven dried 2-5 mL microwave vial was added methyl 1-(phenylsulfonyl)bicyclo[1.1.0]butane (49 mg, 0.25 mmol, 1 eq.), 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 eq.), $Rh(COD)_2BF_4$ and (+/-)-BINAP. The vial was capped and purged, and then 1,4-dioxane (910 µL) and water (90 µL)was added. The reaction was stirred at *temperature* for *time* before being washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. TLC was used to determine if any product was present.

General Procedure HH, investigation into the effect of time, temperature, counterion and catalyst/ligand loading

To an oven dried 2-5 mL microwave vial was added methyl 1-(phenylsulfonyl)bicyclo[1.1.0]butane (49 mg, 0.25 mmol, 1 eq.), 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 eq.), $Rh(COD)_2X$ and (+/-)-BINAP. The vial was capped and purged, and then 1,4-dioxane (910 µL) and water (90 µL) was added. The reaction was stirred at *temperature* for *time* before being washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. TLC was used to determine if any product was present.

6.3 Screening Results

Optimisation of hydroboration using catecholborane (Scheme 43)



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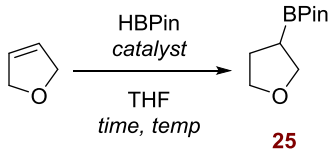
Reactions performed according to General Procedure A using catecholborane (53 µL, 0.5 mmol, 1 eq.).

Entry	Catalyst	Temperature	Time (h)	Yield (%)
1	-	rt	16	0
2	-	40 °C	16	0
3	-	60 °C	16	0
4	-	rt	36	0
5	-	rt	64	0
6	-	40 °C	36	0
7	$Rh(PPh_3)_3Cl$ (4.6 mg)	rt	16	0
8	$Rh(PPh_3)_3Cl$ (4.6 mg)	40 °C	16	0
9	$Rh(PPh_3)_3Cl$ (4.6 mg)	60 °C	16	0
10	$Rh(PPh_3)_3Cl$ (4.6 mg)	rt	48	0
11	$Rh(COD)_2BF_4^-$ (2 mg)	rt	16	0
12	$Rh(COD)_2BF_4^-$ (2 mg)	40 °C	16	0

13	$Rh(COD)_2BF_4^-$ (2 mg)	60 °C	16	0

Optimisation of hydroboration with pinacolborane (Table 1)



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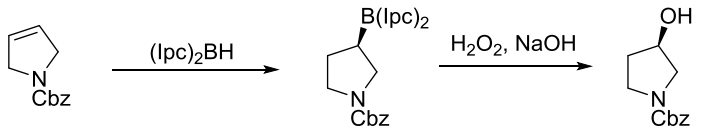
Reactions performed according to General Procedure A using pinacolborane (72 µL, 0.5 mmol, 1 eq.).

Entry	Catalyst	Temperature	Time (h)	Yield (%)
1	-	rt	16	0
2	-	40 °C	16	0
3	-	60 °C	16	0
4	$Rh(PPh_3)_3Cl$ (4.6 mg)	rt	16	55
5	$Rh(PPh_3)_3Cl$ (4.6 mg)	40 °C	16	56
6	$Rh(PPh_3)_3Cl$ (4.6 mg)	60 °C	16	50
7	$Rh(PPh_3)_3Cl$ (4.6 mg)	rt	48	50
8	$Rh(COD)_2BF_4^-$ (2 mg)	rt	16	0
9	$Rh(COD)_2BF_4^-$ (2 mg)	40 °C	16	0
10	$Rh(COD)_2BF_4^-$ (2 mg)	60 °C	16	0
11	$Rh(COD)_2Cl_2$ (2.5 mg)	rt	16	0
12	$Rh(COD)_2Cl_2$ (2.5 mg)	40 °C	16	0

13	$Rh(COD)_2Cl_2$ (2.5 mg)	60 °C	16	0

Hydroboration at varying temperatures (Table 2)



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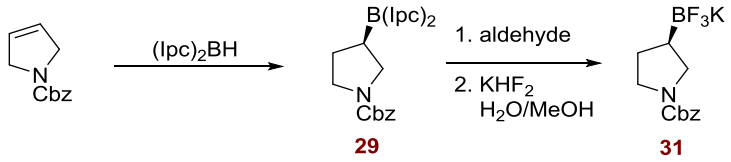
Reactions performed according to General Procedure B.

Entry	Temperature	ee (%)
1	rt	50
2	rt	52
3	rt	65
4	rt	50
5	0 °C	62
6	0 °C	62
7	0 °C	66
8	0 °C	58
9	-25 °C	50
10	-25 °C	60
11	-25 °C	-20
12	-25 °C	20

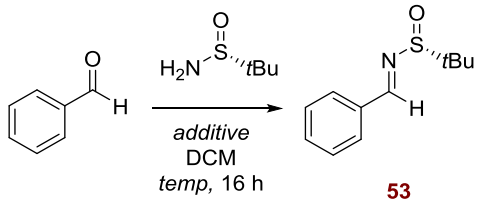
Investigation into the effect of aldehyde towards the formation of BF_3K salt 31 (Table 3)



Reactions performed according to General Procedure C.

Entry	Aldehyde	Yield of 31 (%)
1	Acetaldehyde (84 µL)	7
2	Chloral hydrate (130 µL)	0
3	Benzaldehyde (153 µL)	20 – 32[a,b]
4	Pentafluorobenzaldehyde (185 µL)	21 – 34[a]

Formation of sulfinimine 53 under a range of conditions (Table 4)

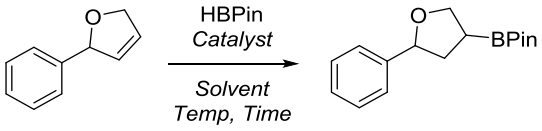


Reactions performed according to General Procedure D.

Entry	Additive	Temperature	Scale (mmol)	Yield (%)
1	$CuSO_4$ (1 eq., 160 mg)	40 °C	1	0
2	Pyrrolidine (0.1 eq., 8 µL)	40 °C	1	93
3	Pyrrolidine (0.1 eq., 16 µL)	40 °C	2	56
4	Pyrrolidine (0.1 eq., 32 µL)	40 °C	4	10

5	Cs_2CO_3 (1 eq., 326 mg)	40 °C	1	93
6	Cs_2CO_3 (1 eq., 1304 mg)	40 °C	4	91
7	Cs_2CO_3 (1 eq., 326 mg)	rt	1	nr

Investigation into the hydroboration of 41 (Table 5)



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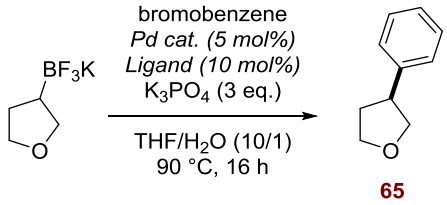
Reactions performed according to General Procedure E.

Entry	Catalyst	Solvent	Temp	Time (h)	Yield (%)
1	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	rt	8	0
2	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	rt	16	0
3	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	rt	48	0
4	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	40	16	0
5	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	40	48	0
6	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	60	16	0
7	$Rh(PPh_3)Cl$ (1 mol%, 2.3 mg)	THF (1 mL)	60	48	0
8	$Rh(PPh_3)Cl$ (5 mol%, 11.5 mg)	THF (1 mL)	rt	16	0

9	$Rh(PPh_3)Cl$ (10 mol%, 23 mg)	THF (1 mL)	rt	16	0
10	$Rh(PPh_3)Cl$ (5 mol%, 11.5 mg)	THF (1 mL)	40	16	0
11	$Rh(PPh_3)Cl$ (10 mol%, 23 mg)	THF (1 mL)	40	16	0
12	$[Rh(COD)Cl]_2$ (1 mol%, 1 mg)	THF (1 mL)	rt	16	0
13	$[Rh(COD)Cl]_2$ (1 mol%, 1 mg)	THF (1 mL)	rt	48	0
14	$[Rh(COD)Cl]_2$ (5 mol%, 6 mg)	THF (1 mL)	40	16	0
15	CuCl (10 mol%, 2.5 mg)	MeOH/THF (0.5 mL/0.5 mL)	rt	16	0
16	CuCl (10 mol%, 2.5 mg)	MeOH/THF (0.5 mL/0.5 mL	40	16	0

Initial SM investigation into the effect of catalyst and ligand (Table 6)



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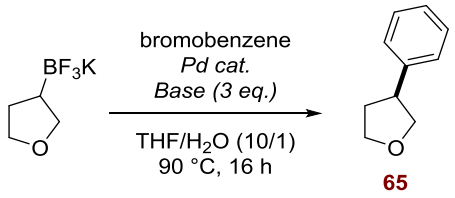
Reactions performed according to General Procedure F using K_3PO_4 (156 mg, 0.75 mmol, 3 eq.), THF (910 µL) and water (90 µL) at 90 °C for 16 h.

Entry	Catalyst	Ligand	Conversion (%)
1	$Pd(OAc)_2$ (2.8 mg)	DavePhos (9.8 mg)	8
2	$Pd(OAc)_2$ (2.8 mg)	XantPhos (14.5 mg)	5
3	$Pd(OAc)_2$ (2.8 mg)	SPhos (10.2 mg)	5

4	$Pd(OAc)_2$ (2.8 mg)	XPhos (11.9 mg)	2
5	$Pd(OAc)_2$ (2.8 mg)	RuPhos (11.6 mg)	0
6	$Pd(OAc)_2$ (2.8 mg)	PPh_3 (6.6 mg)	1
7	$Pd(OAc)_2$ (2.8 mg)	-	0
8	$PdCl_2$ (2.2 mg)	DavePhos (9.8 mg)	0
9	$PdCl_2$ (2.2 mg)	XantPhos (14.5 mg)	14
10	$PdCl_2$ (2.2 mg)	SPhos (10.2 mg)	8
11	$PdCl_2$ (2.2 mg)	XPhos (11.9 mg)	4
12	$PdCl_2$ (2.2 mg)	RuPhos (11.6 mg)	6
13	$PdCl_2$ (2.2 mg)	PPh_3 (6.6 mg)	3
14	$PdCl_2$ (2.2 mg)	-	2
15	$Pd_2(dba)_3$ (11.4 mg)	-	0
16	$Pd_2(dba)_3$ (11.4 mg)	DavePhos (9.8 mg)	0
17	$Pd_2(dba)_3$ (11.4 mg)	XantPhos (14.5 mg)	11
18	$Pd_2(dba)_3$ (11.4 mg)	SPhos (10.2 mg)	0
19	$Pd_2(dba)_3$ (11.4 mg)	XPhos (11.9 mg)	3
20	$Pd_2(dba)_3$ (11.4 mg)	RuPhos (11.6 mg)	4
21	$Pd_2(dba)_3$ (11.4 mg)	PPh_3 (6.6 mg)	1
22	$Pd(dba)_2$ (7.2 mg)	-	36
23	$Pd(dba)_2$ (7.2 mg)	DavePhos (9.8 mg)	0
24	$Pd(dba)_2$ (7.2 mg)	XantPhos (14.5 mg)	11

25	$Pd(dba)_2$ (7.2 mg)	SPhos (10.2 mg)	0
26	$Pd(dba)_2$ (7.2 mg)	XPhos (11.9 mg)	3
27	$Pd(dba)_2$ (7.2 mg)	RuPhos (11.6 mg)	4
28	$Pd(dba)_2$ (7.2 mg)	PPh_3 (6.6 mg)	0
29	$Pd(dppf)Cl_2$.DCM (10.2 mg)	-	11
30	$Pd(PPh_3)_4$ (28.9 mg)	-	9

SM investigation into the effect of base (Table 7)



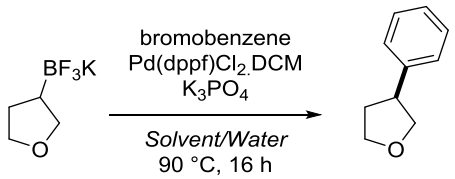
65

Reactions performed according to General Procedure F using THF (910 µL) and water (90 µL) at 90 °C for 16 h.

Entry	Catalyst	Base	Conversion (%)
1	$Pd(PPh_3)_4$ (14.4 mg)	$NaHCO_3$ (63 mg)	10
2	$Pd(PPh_3)_4$ (14.4 mg)	K_3PO_4 (159 mg)	8
3	$Pd(PPh_3)_4$ (14.4 mg)	K_2CO_3 (104 mg)	9
4	$Pd(PPh_3)_4$ (14.4 mg)	KO*t*Bu (84 mg)	2
5	$Pd(PPh_3)_4$ (14.4 mg)	Et_3N (104 µL)	0
6	$Pd(dppf)Cl_2$.DCM (10.2 mg)	$NaHCO_3$ (63 mg)	6
7	$Pd(dppf)Cl_2$.DCM (10.2 mg)	K_3PO_4 (159 mg)	4
8	$Pd(dppf)Cl_2$.DCM (10.2 mg)	K_2CO_3 (104 mg)	6

9	$Pd(dppf)Cl_2$.DCM (10.2 mg)	KO*t*Bu (84 mg)	1
10	$Pd(dppf)Cl_2$.DCM (10.2 mg)	Et_3N (104 µL)	0

Investigation into the effect of water stoichiometry and solvent choice (Table 8)



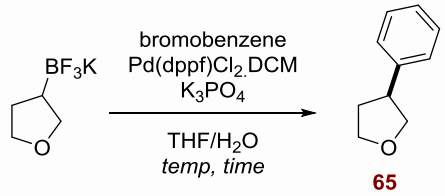
65

Reactions performed according to General Procedure F using K_3PO_4 (156 mg, 0.75 mmol, 3 eq.) and $Pd(dppf)Cl_2$.DCM (20.2 mg, 0.025 mmol, 0.1 eq.) for 16 h at 80 °C.

Entry	Solvent	Water equivalents	Conversion (%)
1	THF	1 (4 µL)	0
2	THF	2 (8 µL)	2
3	THF	6 (24 µL)	6
4	THF	10 (40 µL)	8
5	THF	50 (200 µL)	6
6	THF	100 (400 µL)	2
7	Dioxane	1 (4 µL)	0
8	Dioxane	2 (8 µL)	2
9	Dioxane	6 (24 µL)	5
10	Dioxane	10 (40 µL)	5
11	Dioxane	50 (200 µL)	2
12	Dioxane	100 (400 µL)	0

13	Toluene	6 (24 µL)	1
14	Toluene	10 (40 µL)	2
15	Toluene	50 (200 µL)	0
16	DMF	6 (24 µL)	0
17	DMF	10 (40 µL)	0
18	DMF	50 (200 µL)	0
19	Ethanol	6 (24 µL)	0
20	Ethanol	10 (40 µL)	0
21	Ethanol	50 (200 µL)	0
22	Ethyl Acetate	6 (24 µL)	0
23	Ethyl Acetate	10 (40 µL)	0
24	Ethyl Acetate	50 (200 µL)	0

Investigation into the effect of time and temperature (Table 9)



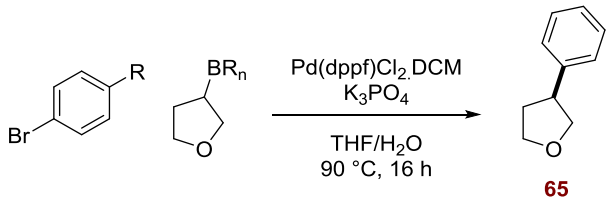
65

Reactions performed according to General Procedure F using K_3PO_4 (156 mg, 0.75 mmol, 3 eq.), Pd(dppf)Cl_2.DCM (20.2 mg, 0.025 mmol, 0.1 eq.), THF (910 µL) and water (90 µL)

Entry	Time	Temperature	Conversion (%)
1	8 h	90 °C	9
2	4 h	90 °C	6

3	2 h	90 °C	6
4	1 h	90 °C	0
5	16 h	50 °C	5
6	8 h	50 °C	6
7	4 h	50 °C	0
8	2 h	50 °C	0
9	1 h	50 °C	0
10	16 h	rt	0
11	8 h	rt	0
12	4 h	rt	0
13	2 h	rt	0
14	1 h	rt	0

Investigation into the effect of changing aryl halide and boron species (Table 10).



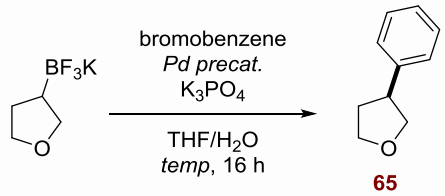
65

Reactions performed according to General Procedure G

Entry	Boron Species	R	Conversion (%)
1	BF_3K	NO_2 (50 mg)	0
2	BF_3K	CO_2Me (54 mg)	0

3	BF_3K	CF_3 (35 µL)	0
4	BPin	NO_2 (50 mg)	0
5	BPin	CO_2Me (54 mg)	0
6	BPin	CF_3 (35 µL)	0

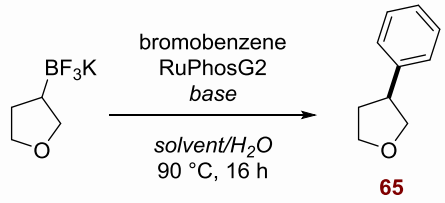
Initial investigations on the use of precatalysts (Table 11)



Reactions performed according to General Procedure F using K_3PO_4 (156 mg, 0.75 mmol, 3 eq.), THF (910 µL) and water (90 µL) at 90 °C for 16 h.

Entry	Precatalyst	Temperature	Conversion (%)
1	DavePhos G2 (8.8 mg)	90	10
2	RuPhos G2 (9.7 mg)	90	20
3	SPhos G2 (9 mg)	90	5
4	XPhos G2 (9.8mg)	90	6
5	DavePhos G2 (8.8 mg)	50	6
6	RuPhos G2 (9.7 mg)	50	15
7	SPhos G2 (9 mg)	50	0
8	XPhos G2 (9.8mg)	50	0

Investigation into variation of solvent, base and water stoichiometry whilst using RuPhosG2 (Table 12)

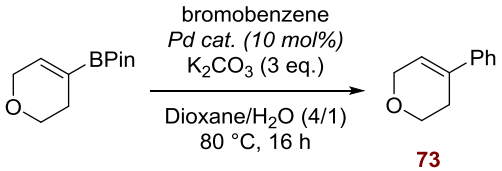


Reactions performed according to General Procedure F using RuPhos G2 (9.7 mg, 0.025 mmol, 0.1 eq.) and THF (1000 µL – water volume) at 90 °C for 16 h.

Entry	Solvent	Water (eq.)	Base	Conversion (%)
1	THF	6 (24 µL)	K_3PO_4 (159 mg)	0
2	THF	10 (40 µL)	K_3PO_4 (159 mg)	2
3	THF	20 (80 µL)	K_3PO_4 (159 mg)	13
4	Dioxane	6 (24 µL)	K_3PO_4 (159 mg)	0
5	Dioxane	10 (40 µL)	K_3PO_4 (159 mg)	2
6	Dioxane	20 (80 µL)	K_3PO_4 (159 mg)	3
7	THF	6 (24 µL)	K_2CO_3 (104 mg)	0
8	THF	6 (24 µL)	$NaHCO_3$ (63 mg)	0

Catalyst screen for SM reaction optimisation (Table 13)

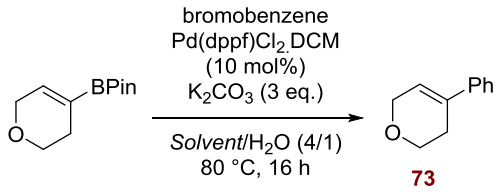
Reactions performed according to general procedure H, using K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) with 1,4-dioxane (950 µL) and water (50 µL) for 4 h.



Entry	Catalyst	Mass of Catalyst (mg)	Conversion (%)
1	$Pd(dba)_2$	14	6
2	$Pd(PPh_3)_4$	29	52
3	$PdCl_2$	4	15
4	$Pd(dppf)Cl_2$.DCM	20	91
5	$Pd(dppf)Cl_2$.DCM	10	92
6	Pd/C	26	36
7	Pd/C	52	39
8	$Pd_2(dba)_3$	23	70

Investigation into the effect of solvent for SM reaction (Table 14)

Reactions performed according to general procedure H, using $Pd(dppf)Cl_2$.DCM (21 mg, 0.025 mmol, 0.1 eq.) for 4 h.

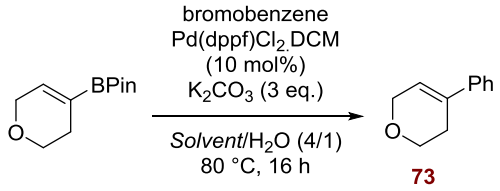


73

Entry	Solvent	Conversion (%)
1	THF	80
2	Dioxane	89
3	Toluene	39
4	EtOH	57
5	EtOAc	50

Investigation into the effect of base for SM reaction (Table 15)

Reactions performed according to general procedure H, using Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.) with dioxane (950 μL) and water (50 μL) for 4 h.

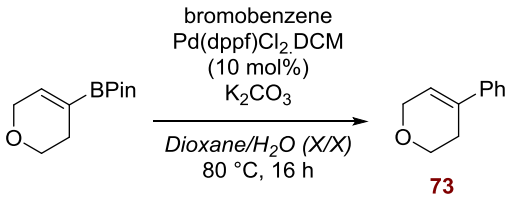


73

Entry	Base	Mass of Base (mg)	Conversion (%)
1	K_2CO_3	104	90
2	K_3PO_4	159	86
3	Cs_2CO_3	244	88
4	K_2CO_3 (dry)	104	88

Investigation into the effect of water stoichiometry for SM reaction (Table 16)

Reactions performed according to general procedure H, using Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) with dioxane (1000 - X μL) and water (X μL) for 4 h.



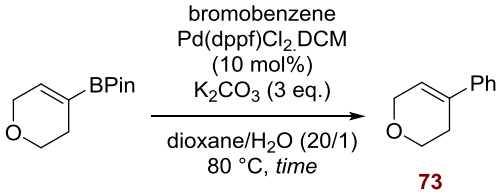
73

Entry	Water	Volume of water (μL)	Conversion (%)
1	1 eq.	4	51

2	5 eq.	20	22
3	12.5 eq.	50	92
4	50 eq.	200	86
5	100 eq.	400	90

Time study for SM reaction optimisation (Table 17)

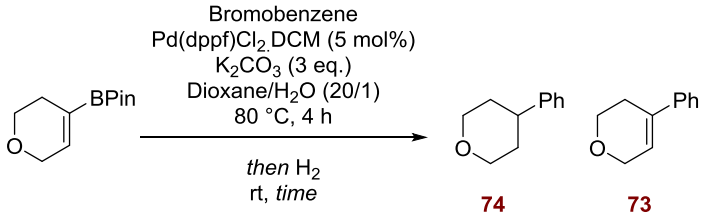
Reactions performed according to general procedure H, using $Pd(dppf)Cl_2$.DCM (21 mg, 0.025 mmol, 0.1 eq.), K_2CO_3 (104 mg, 0.75 mmol, 3 eq.) with dioxane (950 µL) and water (50 µL).



73

Entry	Time (h)	Conversion (%)
1	1	77
2	2	90
3	4	93
4	8	92
5	16	91

Single-pot SM-hydrogenation with Pd(dppf)Cl_2.DCM as the sole palladium source (Scheme 70).

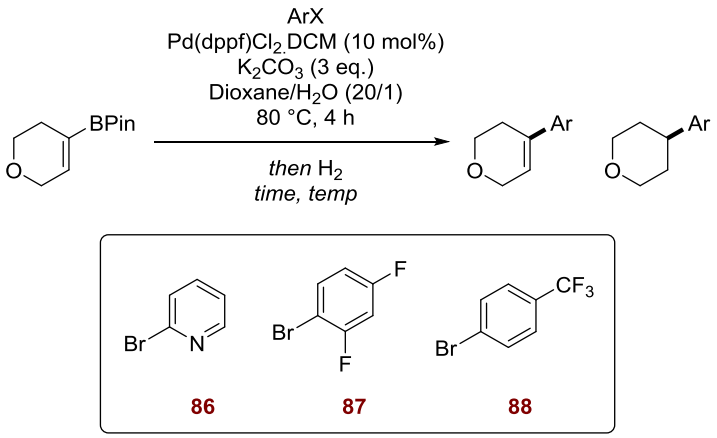


Reactions performed according to general procedure I.

Entry	Time (h)	Catalyst Loading (mol%, mg)	Yield of 74 (%)	Yield of 73 (%)
1	8	5, 10	0	88
2	16	5, 10	60	30
3	4	10, 20	89	0

Investigation into the effect of time and temperature on SM-hydrogenation reaction (Table 18)

Reactions performed according to General Procedure J using a 2-5 mL microwave vial and dioxane.

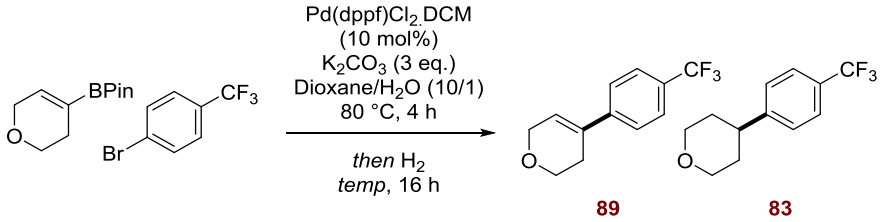


Entry	Aryl Halide	Volume of Aryl Bromide (µL)	Temperature	Time (h)	Hydrogenation (%)

1	86	24	rt	40	0
2	86	24	40 °C	16	0
3	86	24	60 °C	16	0
4	86	24	80 °C	16	0
5	87	28	rt	40	0
6	87	28	40 °C	16	0
7	87	28	60 °C	16	0
8	87	28	80 °C	16	0
9	88	35	rt	40	0
10	88	35	40 °C	16	0
11	88	35	60 °C	16	0
12	88	35	80 °C	16	0

Investigation into the effect of vessel size on the SM-hydrogenation reaction (Table 19)

Reactions performed according to General Procedure J using a 2-5 mL microwave vial, 4-bromobenzotrifluoride (35 µL, 0.25 mmol, 1 equiv) and dioxane.

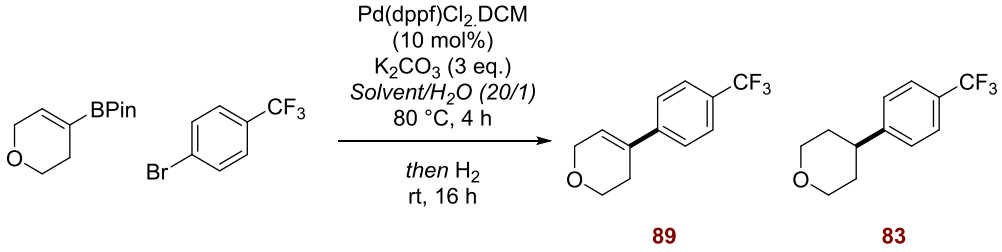


Entry	Reaction Vessel	Temperature	Hydrogenation (%)

1	0.5 – 2 mL microwave vial	rt	0
2	2 – 5 mL microwave vial	rt	0
3	5 mL RBF	rt	0
4	10 mL RBF	rt	5
5	25 mL RBF	rt	10
6	25 mL RBF	40 ^{0}C	10
7	25 mL RBF	60 ^{0}C	10

Investigation into the effect of solvent on the SM-hydrogenation reaction (Table 20)

Reactions performed according to General Procedure J using 2-5 mL microwave vial with bromobenzotrifluoride (35 µL, 0.25 mmol, 1 equiv).

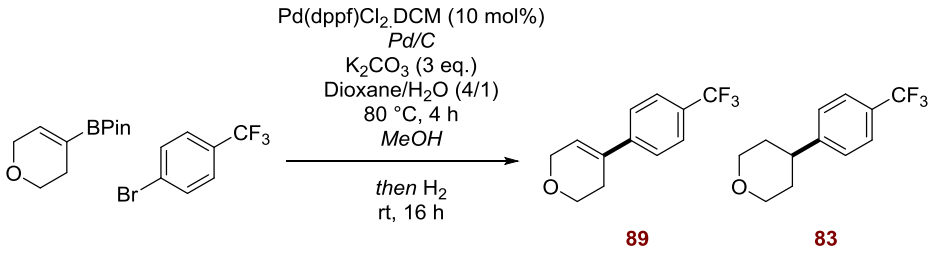


89 83

Entry	Solvent	Hydrogenation (%)
1	*n*-butanol	0
2	3-methyl-2-pentanone	0
3	Ethyl acetate	0

Investigation into the effect of the addition of methanol at various time-points, along with the addition of Pd/C as a co-catalyst (Table 21)

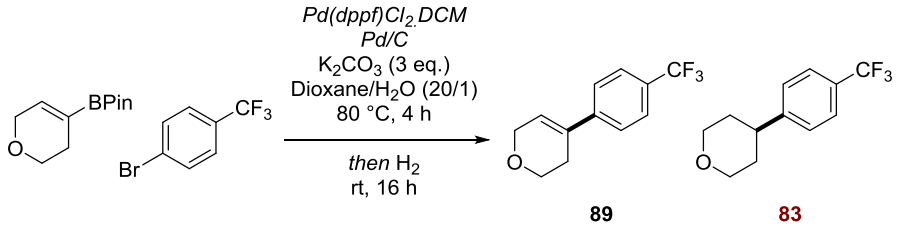
Reactions performed according to General Procedure K using Pd(dppf)Cl_2.DCM (21 mg, 0.025 mmol, 0.1 eq.).



Entry	MeOH (mL)	Addition time (h)	Pd/C	Hydrogenation (%)
1	0.2 mL	0 h	-	0
2	1 mL	0 h	-	0
3	0.2 mL	4 h	-	0
4	1 mL	4 h	-	0
5	2 mL	4 h	-	0
6	0.2 mL	0 h	10 mol% (26 mg)	0
7	1 mL	0 h	10 mol% (26 mg)	0
8	0.2 mL	4 h	10 mol% (26 mg)	0
9	1 mL	4 h	10 mol% (26 mg)	0
10	2 mL	4 h	10 mol% (26 mg)	0

Investigation into the effect of catalyst loading and Pd/C as a co-catalyst (Table 22)

Reactions performed using General Procedure K with no methanol addition.

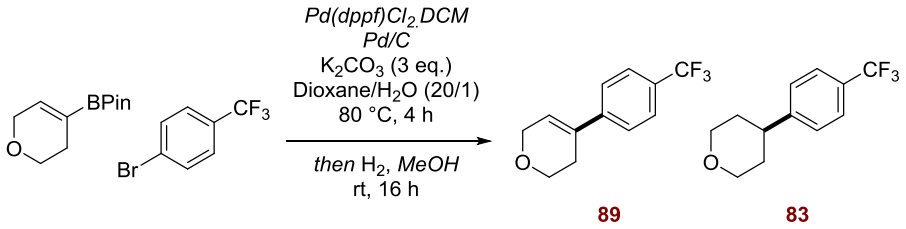


Entry	Pd(dppf)Cl_2.DCM (mol%, mg)	Pd/C (mol%, mg)	Hydrogenation (%)
1	15, 32	0, 0	0
2	20, 42	0, 0	0
3	0, 0	20, 52	100
4	0, 0	10, 26	100
5	5, 11	5, 13	0
6	10, 21	10, 26	0
7	20, 42	20, 52	0
8	2, 4	18, 47	90
9	5, 11	15, 39	90
10	1, 2	9, 23	90
11	2, 4	8, 21	0
12	3, 6	7, 18	0
13	4, 8	6, 16	0
14	5, 10	15, 39	0
15	2, 4	10, 26	10
16	2, 4	12, 31	25

17	2, 4	14, 36	33
18	2, 4	16, 42	80
19	2, 4	20, 52	100

Investigation into the effect of catalyst ratio on hydrogenation with MeOH addition (Table 23)

Reaction performed using General Procedure K using 1 mL of methanol (addition time = 4 h).



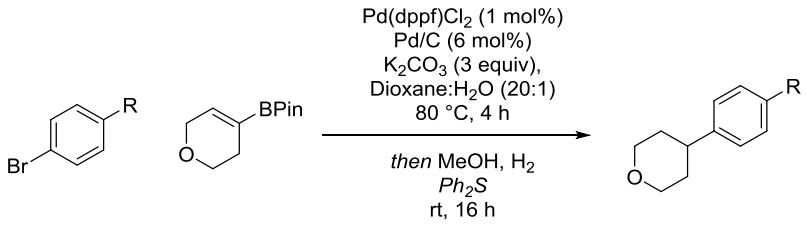
Entry	Pd(dppf)Cl_2.DCM (mol%, mg)	Pd/C (mol%, mg)	% B
1	2, 4	8, 21	90
2	2, 4	10, 26	90
3	2, 4	12, 31	100
4	2, 4	14, 36	100
5	2, 4	16, 42	100
6	2, 4	18, 47	100
7	2, 4	20, 52	100
8	1, 2	6, 16	100

9	2, 4	12, 31	29[a]

a) MeOH was replaced with additional dioxane

Implementation of Sajiki's chemistry on the one-pot procedure under a range of conditions (Table 24)

Reactions performed using General Procedure M using 1 mL of methanol (addition time = 4 h).

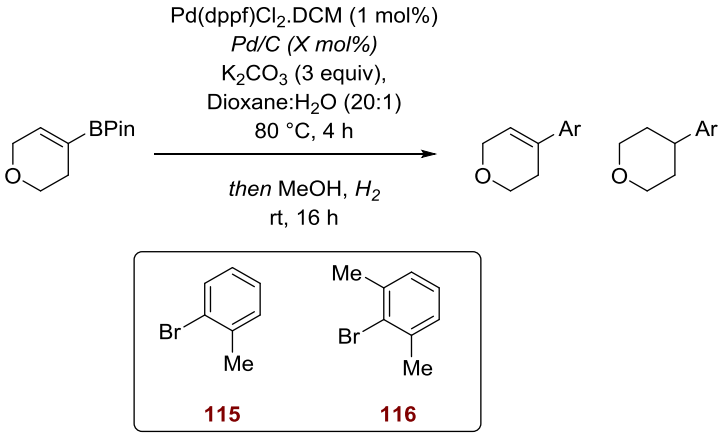


Entry	Ph_2S loading (mol%) and mass	R	Time of Ph_2S addition (h)	Yield
1	10, 5	NHCbz	4	-
2	1, 0.5	NHCbz	4	-
3	10, 5	NHCbz	0	-
4	1, 0.5	NHCbz	0	-
5	10, 5	NHCbz	4	-[a]
6	1, 0.5	OBn	4	-
7	10, 5	OBn	0	-
8	1, 0.5	OBn	0	-
9	1, 0.5	OBn	4	-
10	1, 0.5	OBn	4	-[a]

a) 12 mol% Pd/C used

Investigation into increasing hydrogen pressure on sterically hindered substrates (Table 25)

Reaction performed using General Procedure N.

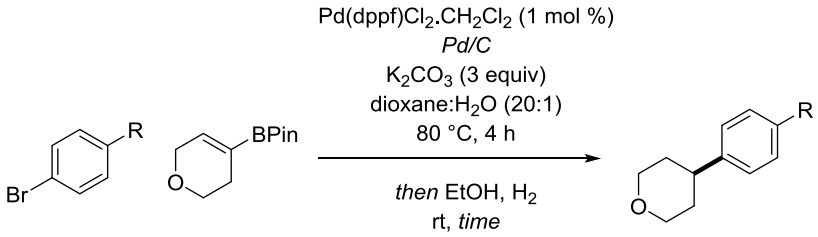


Entry	Aryl Halide	Pd/C (mol%)	Hydrogen Pressure (bar)	% Hydrogenation
1	115	6, 16	Balloon, 1	0
2	116	6, 16	Balloon, 1	0
3	115	10, 26	Balloon, 1	0
4	116	10, 26	Balloon, 1	0
5	115	6, 16	2	0
6	116	6, 16	2	0
7	115	10, 26	2	15
8	116	10, 26	2	23
9	115	10, 26	3	34
10	116	10, 26	3	39
11	115	10, 26	4	42

12	116	10, 26	4	50

Examination of ethanol as a co-solvent (Table 26)

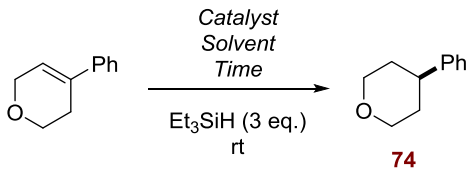
Reaction performed using General Procedure O.



Entry	Aryl Halide	Pd/C (mol%, mg)	EtOH (mL)	Time (h)	Hydrogenation (%)	Yield (%)
1	H	6, 16	1	16	100	91
2	CF_3	6, 16	1	16	20	-
3	NO_2	6, 16	1	16	50	-
4	CF_3	10, 26	1	16	25	-
5	NO_2	10, 26	1	16	55	-
6	CF_3	10, 26	2	48	100	90
7	NO_2	10, 26	2	48	80	-

Initial investigation into TH reaction using triethylsilane (Table 27)

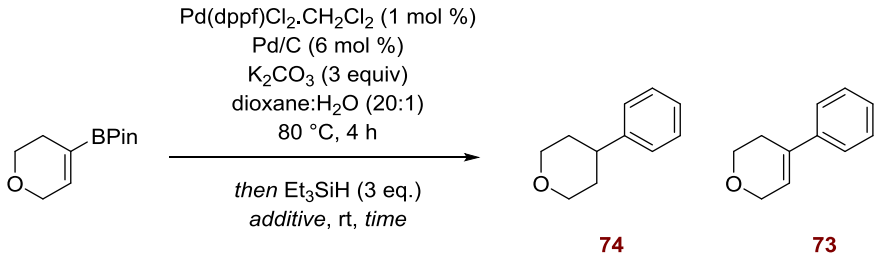
Reactions performed according to General Procedure P.



Entry	Catalyst	Loading (mol%), mass (mg)	Solvent	Time	% Hydrogenation
1	Pd/C	10, 26	MeOH	16 h	100
2	Pd/C	5, 14	MeOH	16 h	100
3	$Pd(dppf)Cl_2$.DCM	1, 2	MeOH	16 h	0
4	$Pd(dppf)Cl_2$.DCM	5, 10	MeOH	16 h	16
5	Pd/C	6, 16	Dioxane	16 h	100
6	Pd/C	6, 16	Dioxane	30 min	100
7	Pd/C	6, 16	Dioxane	5 min	100
8	Pd/C	6, 16	Dioxane	3 min	100
9	Pd/C	6, 16	Dioxane	1 min	87

Application of TH conditions to the one-pot procedure (Table 28)

Reactions performed according to General Procedure Q.



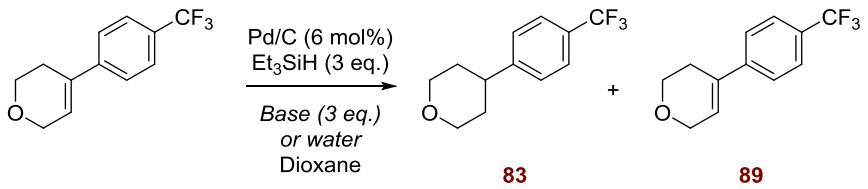
74 73

Entry	Additive	Time	Hydrogenation (%)
1	MeOH	16 h	100
2	-	16 h	0
3	MeOH	1 h	0

4	EtOH	16 h	0

Investigation into the effect of base and water on the TH aspect of the reaction (Table 29)

Reactions performed according to General Procedure R.

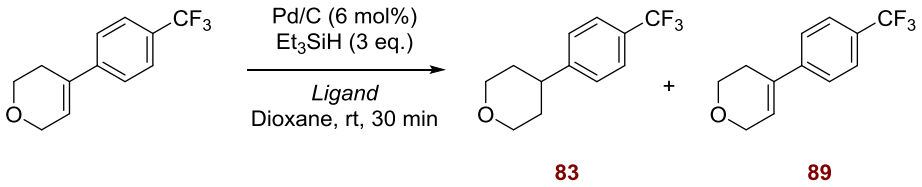


83 89

Entry	Additive	Weight/Volume	Hydrogenation (%)
1	K_2CO_3	104 mg	24
2	K_2CO_3	104 mg	22
3	K_3PO_4	159 mg	25
4	Na_2CO_3	80 mg	55
5	$CaCO_3$	75 mg	100
6	Cs_2CO_3	264 mg	0
7	NaOH	30 mg	28
8	Et_3N	104 µL	12
9	Water	100 µL	100

Investigation into the effect of added ligand to the transfer hydrogenation (Table 30)

Reactions performed according to General Procedure S.



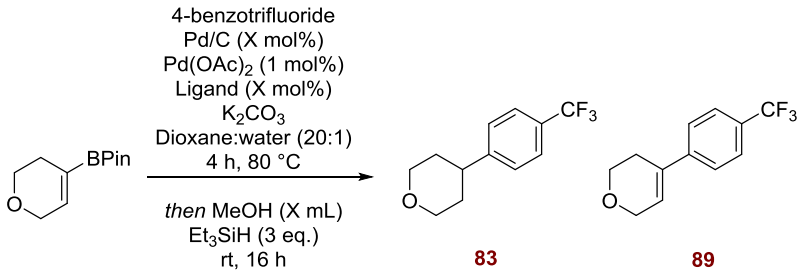
83 89

Entry	Ligand	Loading and weight (mol%, mg)	Hydrogenation (%)
1	$Pd(dppf)Cl_2$.DCM	1, 2	83
2	$Pd(dppf)Cl_2$.DCM	12, 24	44
3	dppf	1, 1.3	93
4	dppf	12, 17	8
5	dppf	3, 4	30
6	DavePhos	3, 3.0	100
7	JohnPhos	3, 2.2	100
8	BrettPhos	3, 4	100
9	RuPhos	3, 3.5	100
10	XPhos	3, 3.6	100
11	BINAP	3, 4.7	85
12	JosiPhos	3, 4.8	78
13	XantPhos	3, 4.3	63
14	dppp	3, 3.1	0
15	APhos	3, 2	66

16	SPhos	3, 3	66

Application of successful ligands to the one-pot, two-step process (Table 31)

Reactions performed according to General Procedure T.

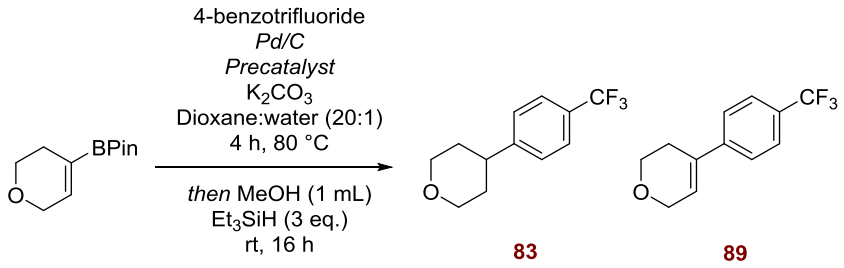


Entry	Ligand	Ligand Loading and Weight (mol%, mg)	Pd/C Loading and Weight (mol%, mg)	Hydrogenation (%)
1	DavePhos	2, 1.5	6, 16	22
2	BrettPhos	2, 2.7	6, 16	62
3	RuPhos	2, 2.3	6, 16	28
4	BrettPhos	2, 2.7	6, 16	-[a]
5	RuPhos	2, 2.3	6, 16	59
6	BrettPhos	2, 2.7	10, 26	100
7	RuPhos	2, 2.3	10, 26	100
8	BrettPhos	1, 1.3	6, 16	79
9	RuPhos	1, 1.2	6, 16	56

a) Unable to determine extent of hydrogenation by ^{1}H NMR

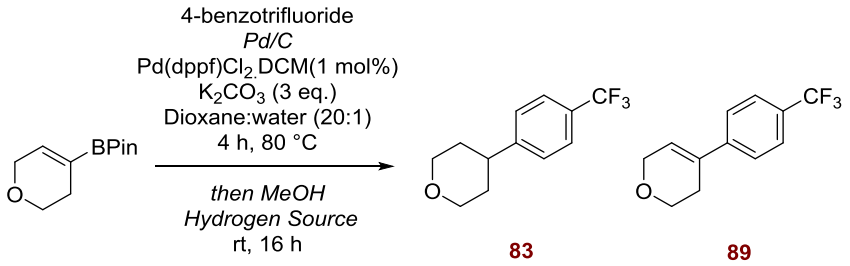
Application of precatalysts in to the two-step, one-pot process (Table 32)

Reactions performed according to General Procedure U.



Entry	Precatalyst	Pd/C Loading and Amount (mol%, mg)	Hydrogenation (%)
1	Xphos G2 (2 mg)	6, 16	41
2	RuPhos G2 (2 mg)	6, 16	26
3	BrettPhos G3 (2.3 mg)	6, 16	36
4	Xphos G2 (2 mg)	10, 26	61
5	RuPhos G2 (2 mg)	10, 26	30
6	BrettPhos G3 (2.3 mg)	10, 26	62

Catalyst loading and hydrogen source investigation (Table 33)

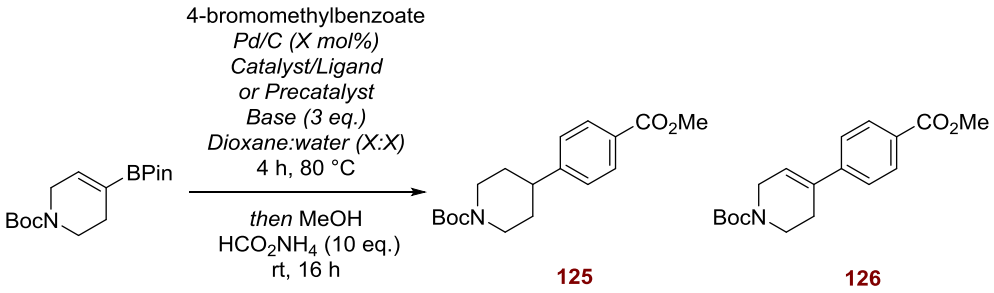


Reactions performed according to General Procedure V with varying hydrogen sources shown below.

Entry	Hydrogen Source	Pd/C Loading (mol%)	MeOH (mL)	Hydrogenation (%)

1	Et_3SiH (120 µL)	15	1	72
2	Et_3SiH (120 µL)	20	1	76
3	Et_3SiH (120 µL)	20	2	100
4	HCO_2NH_4 (158 mg)	10	1	57
5	HCO_2NH_4 (158 mg)	10	2	100

Further optimisation of SM-TH conditions (Table 34)



Reactions performed according to General Procedure X.

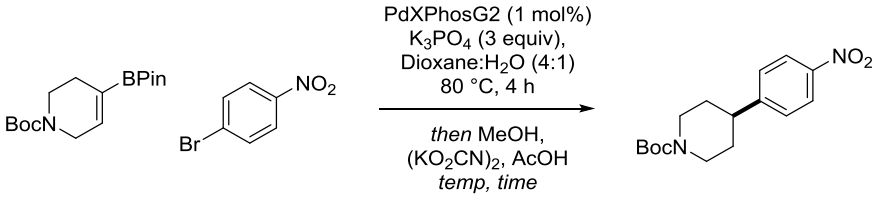
Entry	Catalyst/Precatalyst (mol%, mg)	Pd/C (mol%, mg)	Base	Dioxane:H_2O	Hydrogenation (%)	Yield (%)
1	$Pd(OAc)_2$/XPhos (1, 0.5/2, 2)	10, 26	K_2CO_3 (103 mg)	20:1	18	38
2	$Pd(OAc)_2$/XPhos (2, 1/4, 4)	20, 52	K_2CO_3 (103 mg)	20:1	24	51
3	$Pd(OAc)_2$/XPhos (2, 1/4, 4)	20, 52	K_2CO_3 (103 mg)	20:1	-	50
4	$Pd(OAc)_2$/XPhos (3, 1.5/3, 3)	20, 52	K_2CO_3 (103 mg)	20:1	43	83

5	$Pd(OAc)_2$/XPhos (4, 2/4, 4)	20, 52	K_2CO_3 (103 mg)	20:1	43	89
6	XPhos G2 (1, 2)	8, 21	K_2CO_3 (103 mg)	20:1	53	-[a]
7	XPhos G2 (1, 2)	10, 26	K_2CO_3 (103 mg)	20:1	80	-[a]
8	XPhos G2 (1, 2)	12, 32	K_2CO_3 (103 mg)	20:1	100	81
9	XPhos G2 (1, 2)	12, 32	K_3PO_4 (159 mg)	20:1	100	90
10	XPhos G2 (1, 2)	12, 32	K_3PO_4 (159 mg)	4:1	100	>99%

a) not isolated

Investigation into olefin reduction of trisubstituted alkene using potassium azodicarboxylate (Table 35)

Reactions performed according to General Procedure X.



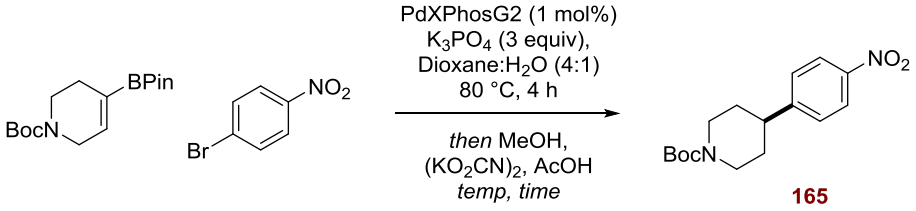
Entry	Time (h)	Temp	Eq. of $(KO_2CN)_2$	Vessel	% Hydrogenation
1	4	rt	20 (965 mg)	microwave vial	0
2	16	rt	20 (965 mg)	microwave vial	0
3	16	50 °C	20 (965 mg)	microwave vial	0

4	16	rt	30 (1448 mg)	microwave vial	0

a) work-up performed after SM reaction

Investigation into olefin reduction of disubstituted alkene using potassium azodicarboxylate (Table 36)

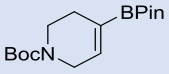
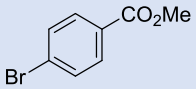
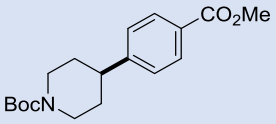
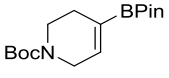
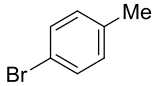
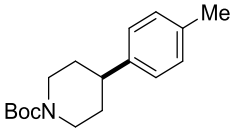
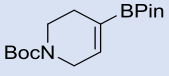
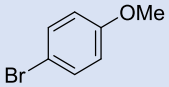
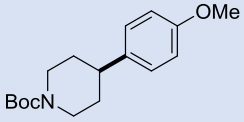
Reactions performed according to General Procedure Y.

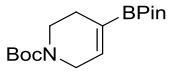
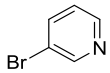
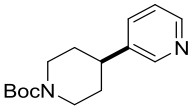
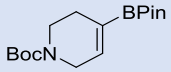
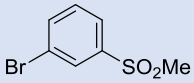
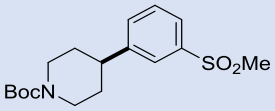
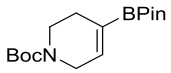
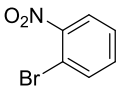
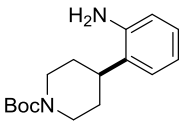
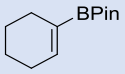
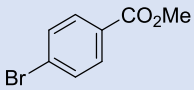
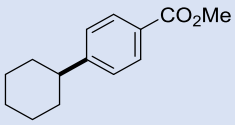
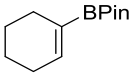
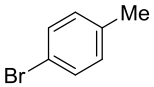
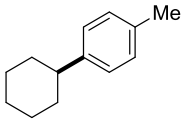
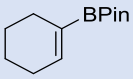
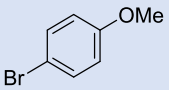
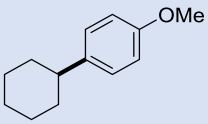
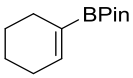
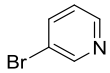
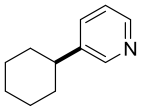
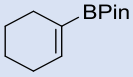
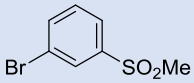
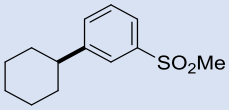
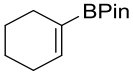
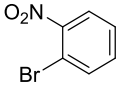
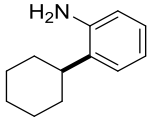
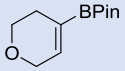
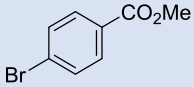
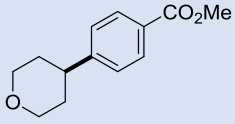
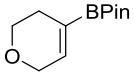
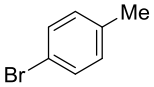
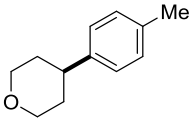
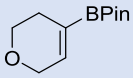
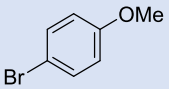
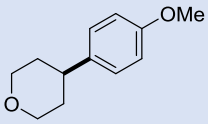
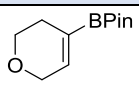
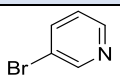
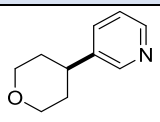


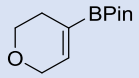
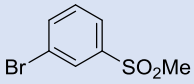
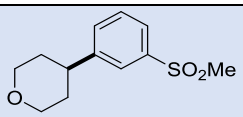
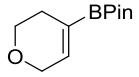
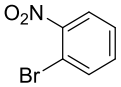
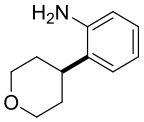
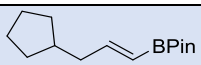
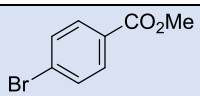
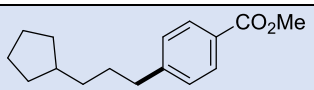
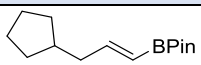
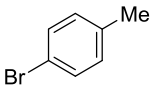
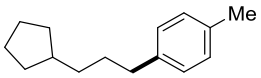
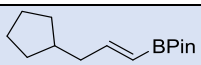
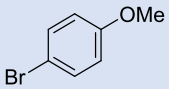
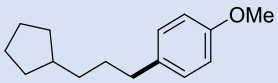
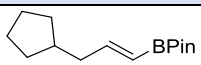
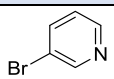
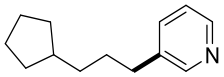
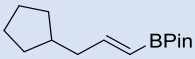
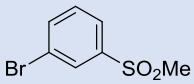
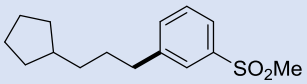
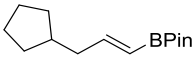
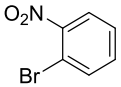
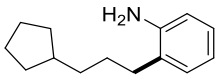
Entry	Time (h)	Temp	Eq. of $(KO_2CN)_2$	% Hydrogenation
1	16	rt	20 (965 mg)	62
2	16	50 °C	20 (965 mg)	44
3	16	rt	30 (1448 mg)	59
4	40	rt	20 (965 mg)	65

Array synthesis application (Scheme 91)

Reactions performed according to General Procedure Z.

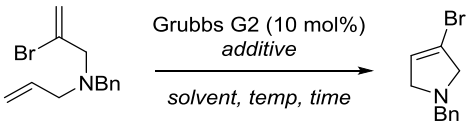
Entry	BPin	Aryl Halide	Product	Conversion
1	 39 mg	 26 mg		98%
2	 39 mg	 16 µL		Quant.
3	 39 mg	 16 µL		94%

4	 39 mg	 12 µL		79%
5	 39 mg	 30 mg		99%
6	 39 mg	 26 mg		95%
7	 26 mg	 26 mg		95%
8	 26 mg	 16 µL		80%
9	 26 mg	 16 µL		79%
10	 26 mg	 12 µL		54%
11	 26 mg	 30 mg		64%
12	 26 mg	 26 mg		71%
13	 27 mg	 26 mg		86%
14	 27 mg	 16 µL		75%
15	 27 mg	 16 µL		62%
16	 27 mg	 12 µL		66%

17	 27 mg	 30 mg		54%
18	 27 mg	 26 mg		69%
19	 30 mg	 26 mg		98%
20	 30 mg	 16 µL		58%
21	 30 mg	 16 µL		70%
22	 30 mg	 12 µL		38%
23	 30 mg	 30 mg		50%
24	 30 mg	 26 mg		-

RCM attempts to synthesis vinyl bromide with benzyl protected amine (Scheme 97)

Reactions performed according to General Procedure BB.

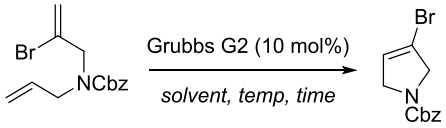


Entry	Acid	Time (h)	Temperature (°C)	Solvent	Yield (%)
1	-	4	rt	DCM	-
2	-	4	40	DCM	-
3	-	16	rt	DCM	-

4	-	16	40	DCM	-
5	TFA, 29 µL	16	rt	DCM	-
6	TFA, 29 µL	16	40	DCM	-
7	(+)-CSA, 87 mg	16	rt	DCM	-
8	(+)-CSA, 87 mg	16	40	DCM	-
9	(+)-CSA, 87 mg	16	100	toluene	-

RCM attempts to synthesis vinyl bromide with Cbz protected amine (Scheme 98)

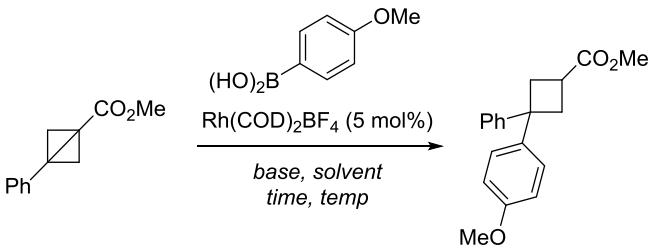
Reactions performed according to General Procedure CC.



Entry	Grubbs' G2 (mol%, mg)	Time (h)	Temperature (°C)	Solvent	Yield (%)
1	10, 20	4	rt	DCM	-
2	10, 20	4	40	DCM	-
3	10, 20	16	rt	DCM	-
4	10, 20	16	40	DCM	-
5	20, 40	16	rt	DCM	-
6	10, 20	16	100	toluene	-

Initial investigative reactions into the addition of 4-methoxyboronic acid into 206 (Table 37)

Reactions performed according to General Procedure DD.



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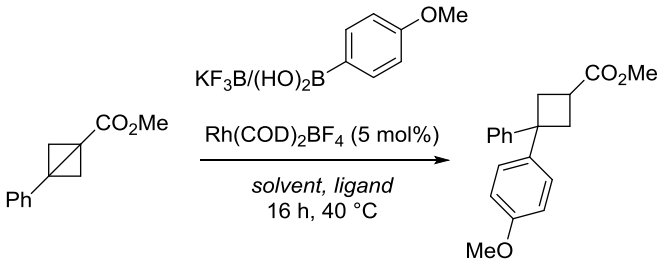
Entry	Temp	Time (h)	Solvent	Base (mg)	Yield (%)
1	rt	16	Dioxane	-	0
2	rt	16	Dioxane:H_2O (10:1)	-	0
3	rt	16	Dioxane:H_2O (10:1)	KOH (42)	0
4	40 °C	16	Dioxane	-	0
5	40 °C	16	Dioxane:H_2O (10:1)	-	0
6	40 °C	16	Dioxane:H_2O (10:1)	KOH (42)	0
7	90 °C	16	Dioxane	-	0
8	90 °C	2	Dioxane	-	0
9	90 °C	8	Dioxane	-	0
10	90 °C	8	Dioxane:H_2O (10:1)	-	0
11	90 °C	8	Dioxane:H_2O (10:1)	KOH (42)	0

Investigation into the effect of boron species, solvent, water and ligand (Table 38)

Reactions performed according to General Procedure EE.



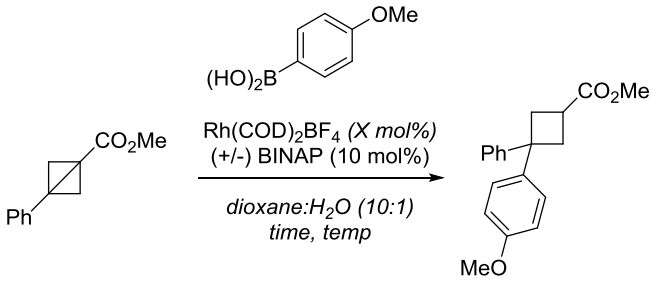
207

Entry	Boron	Solvent	Water (µL)	Ligand	Yield (%)
1	$B(OH)_2$	Dioxane	1 eq. (4)	-	0
2	$B(OH)_2$	Dioxane	2 eq. (8)	-	0
3	$B(OH)_2$	Dioxane	5 eq. (20)	-	0
4	$B(OH)_2$	Dioxane	10 eq. (40)	-	0
5	BF_3K	Dioxane	10:1	-	0
6	BF_3K	Dioxane	10:1	-	0
7	$B(OH)_2$	Dioxane	10:1	(+/-) BINAP	9
8	$B(OH)_2$	THF	10:1	-	0
9	BF_3K	THF	10:1	-	0
10	$B(OH)_2$	THF	10:1	-	0[a]
11	$B(OH)_2$	THF	10:1	(+/-) BINAP	0

a) Reaction performed at 70 °C

Investigation into the effect of time, temperature and catalyst loading (Table 39)

Reactions performed according to General Procedure FF.

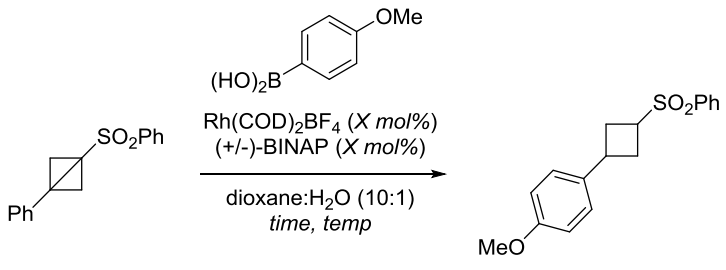


207

Entry	Time (h)	Temperature (°C)	Catalyst Loading (mol%, mg)	Yield (%)
1	16	rt	5, 5	0
2	48	40	5, 5	10
3	72	40	5, 5	7
4	16	100	5, 5	0
5	48	100	5, 5	0
6	16	40	10, 10	10

Investigation into the effect of time, temperature and catalyst/ligand loading using sulfone 213 (Table 40)

Reactions performed according to General Procedure GG.

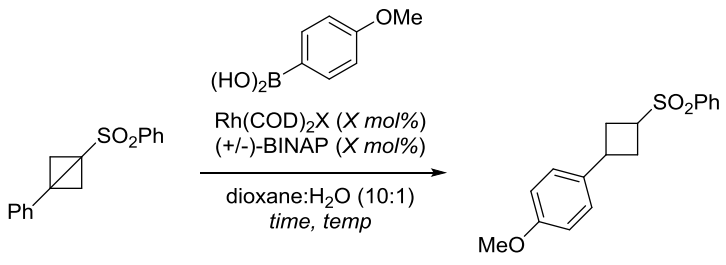


214

Entry	Time (h)	Temperature (°C)	Catalyst (mol%, mg)	Ligand Loading (mol%, mg)	Yield (%)
1	8	rt	5, 5	10, 16	0
2	8	rt	10, 10	20, 32	0
3	16	rt	5, 5	10, 16	0
4	8	40	5, 5	10, 16	0
5	8	40	10, 10	20, 32	0
6	16	40	5, 5	10, 16	0
7	8	60	5, 5	10, 16	0
8	8	60	10, 10	20, 32	0
9	16	60	5, 5	10, 16	0
10	8	80	5, 5	10, 16	0
11	8	80	10, 10	20, 32	0
12	16	80	5, 5	10, 16	0

Investigation into the effect of time, temperature, counterion and catalyst/ligand loading (Table 41)

Reactions performed according to General Procedure HH.

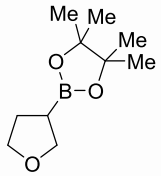


214

Entry	Time (h)	Temperature (°C)	Counterion of Catalyst (mol%, mg)	Ligand (mol%, mg)	Yield (%)
1	16	80	BF_4, 10, 10	20, 32	0
2	36	80	BF_4, 5, 5	10, 16	0
3	16	100	BF_4, 5, 5	10, 16	0
4	16	100	BF_4, 10, 10	20, 32	0
5	36	100	BF_4, 5, 5	10, 16	0
6	36	100	BF_4, 10, 10	20, 32	0
7	16	80	Cl, 10, 12	20, 32	0
8	36	80	Cl, 5, 6	10, 16	0
9	16	100	Cl, 5, 6	10, 16	0
10	16	100	Cl, 10, 12	20, 32	0
11	36	100	Cl, 5, 6	10, 16	0
12	36	100	Cl, 10, 12	20, 32	0,

6.4 Characterisation Data for Isolated Products

Compound 25, 4,4,5,5-tetramethyl-2-(tetrahydrofuran-3-yl)-1,3,2-dioxaborolane



A solution of $Rh(PPh_3)_3Cl$ (4.6 mg, 0.05 mmol, 0.1 eq.) in anhydrous THF (1 mL) was sonicated for 5 minutes in an open round bottom flask. Following this, the flask was sealed and purged several times with nitrogen. Pinacolborane (72 µL, 0.5 mmol, 1 eq.).was added and the reaction mixture was stirred for 5 minutes under nitrogen at room temperature. 2,5 dihydrofuran (37 µL, 0.5 mmol, 1 eq.) was added dropwise and the reaction mixture was stirred at room temperature under nitrogen for 16 h. The reaction was subsequently diluted with ethyl acetate and washed through Celite with further ethyl acetate. The crude material was purified by flash chromatography (10% EtOAc/PE) to afford title compound as a clear oil (54 mg, 55%).

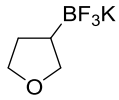
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (t, 1H, *J* = 8.3 Hz,), 3.83 (td, 1H, *J* = 8.1, 4.2 Hz), 3.76 – 3.68 (m, 1H), 3.64 (dd, 1H, *J* = 9.7, 8.1 Hz), 2.11 – 2.01 (m, 1H), 1.91 – 1.79 (m, 1H), 1.60 (quin, 1H, *J* = 6.6 Hz), 1.27 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 83.4, 70.3, 68.5, 28.7, 24.7

HRMS ($C_{10}H_{20}BO_3$) $[M+H]^+$ requires 199.1500, found 199.1499

Consistent with reported data.[212]

Compound 26, trifluoro(tetrahydrofuran-3-yl)-l4-borane, potassium salt



To a solution of 4,4,5,5-tetramethyl-2-(tetrahydrofuran-3-yl)-1,3,2-dioxaborolane (198 mg, 1 mmol, 1 eq.) in MeOH (1 mL) was added KHF_2 (4.5 M in water) (312 mg, 4 mmol, 4 eq.). The reaction mixture was stirred at room temp for 4 h before being concentrated *in vacuo*. The subsequent white solid was extracted three times with MeOH:Acetone (4:1, 10 mL) which was concentrated *in vacuo* until a precipitate began to appear. At this point, Et_2O was added to the

mixture until the trifluoroborate salt precipitated from solution. Filtration afforded the title compound as a white solid (123 mg, 69%).

^{1}H NMR (400 MHz, DMSO): δ 3.64 (t, 1H, CH, *J* = 8.0 Hz), 3.54 (td, 1H, CH, *J* = 7.8, 3.2 Hz), 3.42 – 3.35 (m, 1H, CH), 3.23 (dd, 1H, CH, *J* = 11.0, 7.5 Hz), 1.67 – 1.58 (m, 1H, CH), 1.47 (dt, 1H, CH, *J* = 20.1, 10.1 Hz), 0.79 (br. s, 1H, CH).

^{13}C NMR (126 MHz, DMSO): δ 71.4, 67.4, 29.0 (1C not observed).

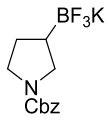
^{11}B NMR (128 MHz, DMSO) δ 4.2

^{19}F NMR (376 MHz, DMSO) δ -140.8

HRMS ($C_4H_7BF_3O$) $[M\text{-}K]^-$ requires 139.0548, found 139.0550

Consistent with reported data.[213]

Compound 28, benzyl 3-(trifluoro--boranyl)pyrrolidine-1-carboxylate, potassium salt



A solution of $Rh(PPh_3)_3Cl$ (4.6 mg, 0.05 mmol, 0.1 eq.) in anhydrous THF (1 mL) was sonicated for 5 minutes in an open round bottom flask. Following this, the flask was sealed and purged several times with nitrogen. Pinacolborane (72 µL, 0.5 mmol, 1 eq.).was added and the reaction mixture was stirred for 5 minutes under nitrogen at room temperature. benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (100 mg, 0.5 mmol, 1 eq.) was added dropwise and the reaction mixture was stirred at room temperature under nitrogen for 16 h. The reaction was subsequently diluted with ethyl acetate and washed with water, and then dried with Na_2SO_4. The crude material dissolved in MeOH (1 mL) and KHF_2 (4.5 M in water) (312 mg, 4 mmol, 4 eq.) was added. The reaction mixture was stirred at room temp for 4 h before being concentrated *in vacuo*. The subsequent white solid was extracted three times with MeOH:Acetone (4:1, 10 mL) which was concentrated *in vacuo* until a precipitate began to appear. At this point, Et_2O was added to the mixture until the trifluoroborate salt precipitated from solution. Filtration afforded the title compound as a white solid (64 mg, 41%).

^{1}H NMR (400 MHz, DMSO): δ 7.32 – 7.25 (m, 4H, 4 x ArH), 7.22 – 7.17 (m, 1H, ArH), 5.36 (s, 2H, CH_2), 3.52 – 3.42 (m, 2H, 2 x CH), 3.10 – 2.95 (m, 2H, 2 x CH), 1.76 – 1.55 (m, 2H, 2 x CH), 1.20-1.00 (m, 1H, CH).

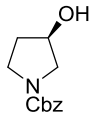
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 137.0, 136.8, 128.1, 128.0, 71.5, 50.5, 50.1, 49.2, 48.3.

^{11}B NMR (128 MHz, DMSO) δ 4.5

^{19}F NMR (376 MHz, DMSO) δ -146.8

Consistent with reported data.[213]

Compound 32, benzyl (*R*)-3-hydroxypyrrolidine-1-carboxylate



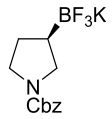
To an oven dried round bottom flask was added (-)-α-pinene (155 µL, 1 mmol, 1 eq.) and dry THF (1 mL), and the mixture was cooled to -78 °C. BH_3.DMS (1M in THF, 2 mL, 2 mmol, 2 eq.) was added dropwise and the reaction was stirred at -78 °C for 8 h. Following this, the mixture was allowed to sit undisturbed at 5 °C for 3 days. At this point, the solvent was removed using a needle and the resulting white solid was washed with dry Et_2O before being dried under vacuum. The solid was dissolved in dry THF and cooled to -25 °C before benzyl benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (152 mg, 0.75 mmol, 0.75 eq.) was added dropwise in dry THF (1 mL). The reaction was stirred at -25 °C for 8 hours before being warmed to 0 °C and NaOH (200 mg, 5 mmol, 5 eq.) and H_2O_2 (30% in water, 783 µL, 10 mmol, 10 eq.) were added and stirred for 2 h. The reaction was washed between Et_2O and sodium metabisulfite (aq.) solution. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H, 5 x ArH), 5.16 (s, 2H, CH_2), 4.40 (s, 1H, CH), 3.66 – 3.55 (m, 3H, 3 x CH), 3.54 – 3.49 (m, 1H, CH), 2.80-2.77 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0, 137.0, 128.3, 128.0, 70.9, 67.1, 54.7, 44.0, 33.8 (1C not observed).

Consistent with reported data. [214]

Compound 32, benzyl (*R*)-3-(trifluoro-boranyl)pyrrolidine-1-carboxylate, potassium salt



To an oven dried round bottom flask was added (-)-α-pinene (155 µL, 1 mmol, 1 eq.) and dry THF (1 mL), and the mixture was cooled to -78 °C. BH_3.DMS (1M in THF, 2 mL, 2 mmol, 2 eq.) was added dropwise and the reaction was stirred at -78 °C for 8 h. Following this, the mixture was allowed to sit undisturbed at -20 °C for 3 days. At this point, the solvent was removed using a needle and the resulting white solid was washed with dry Et_2O before being dried under vacuum. The solid was dissolved in dry THF and cooled to -78 °C before benzyl benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (152 mg, 0.75 mmol, 0.75 eq.) was added dropwise in dry THF (1 mL). The reaction was stirred at -78 °C for 8 hours before being warmed to 0 °C and benzaldehyde (1 eq.) in dry THF (1 mL) was added dropwise. After being stirred at room temperature for 4 hours, KHF_2 (4.5 M in water) (312 mg, 4 mmol, 4 eq.) and MeOH (1 mL) were added and the reaction was stirred at room temperature for 16 h. Following concentration *in vacuo*, the subsequent white solid was extracted three times with MeOH:Acetone (4:1, 10 mL) which was concentrated *in vacuo* until a precipitate began to appear. At this point, Et_2O was added to the mixture until the trifluoroborate salt precipitated from solution. Filtration afforded the title compound as a white solid.

^{1}H NMR (400 MHz, DMSO): δ 7.32 – 7.25 (m, 4H, 4 x ArH), 7.22 – 7.17 (m, 1H, ArH), 5.36 (s, 2H, CH_2), 3.52 - 3.42 (m, 2H, 2 x CH), 3.10 – 2.95 (m, 2H, 2 x CH), 1.76 – 1.55 (m, 2H, 2 x CH), 1.20-1.00 (m, 1H, CH).

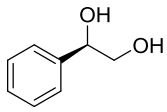
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 137.0, 136.8, 128.1, 128.0, 71.5, 50.5, 50.1, 49.2, 48.3.

^{11}B NMR (128 MHz, DMSO) δ 4.5

^{19}F NMR (376 MHz, DMSO) δ -146.8

Consistent with reported data.[213]

Compound 33, (*R*)-1-phenylethane-1,2-diol



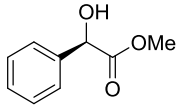
To a solution of (*R*)-mandelic acid (152 mg, 1 mmol, 1 eq.) in dry THF (1 mL) was added BH_3.THF (1M in THF) (6 mL, 6 mmol, 6 eq.) dropwise at 0 °C. The reaction was stirred at room temperature for 16 h, then it was quenched with water. The mixture was washed between water and ethyl acetate, dried with Na_2SO_4, then concentrated *in vacuo* to afford the title compound as a white amorphous solid (110 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.39 (m, 5H, 5 x ArH), 4.84 – 4.82 (1H, m, CH), 3.70 (br. s, 1H, CH), 3.64 (br. s, 1H, CH). 2H not observed, exchangeable.

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 128.5, 128.1, 126.2, 75.0, 68.0

Commercially available compound (CAS: 25779-13-9), consistent with reported data.[215]

Compound 35, methyl (*R*)-2-hydroxy-2-phenylacetate

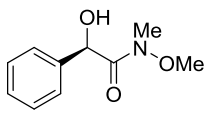


To a solution of (*R*)-mandelic acid (304 mg, 2 mmol, 1 eq.) in methanol (10 mL) was added $SOCl_2$ (2 mL) at 0 °C. The solution was refluxed for 2 hours before being quenched with water, and then washed between ethyl actate and 1 M NaOH (aq.). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white amorphous solid (319 mg, 96%). The compound was telescoped to the next step – ^{1}H NMR was acquired to confirm the identity of this intermediate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 5H), 5.18 – 5.15 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.10 (d, 1H, J = 5.4 Hz).

Commercially available compound (CAS: 20698-91-3), consistent with reported data.[216]

Compound 36, (*R*)-2-hydroxy-*N*-methoxy-*N*-methyl-2-phenylacetamide

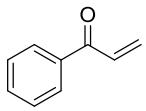


To a solution of (*R*)-mandelic acid (304 mg, 2 mmol, 1 eq.) in DCM (8 mL) was added HATU (836, 2.2 mmol, 1.1 eq.) and DIPEA (695 µL, 4 mmol, 2 eq.) at 0 °C. After 30 minutes of stirring at room temp, *N*,*O*-dimethylhydroxylamine hydrochloride (216, 2.2 mmol, 1.1 eq.). The reaction was stirred at room temperature for 20 hours before being washed between 1 M HCl and DCM, then 1 M NaOH and DCM. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white amorphous solid (300 mg, 77%). The compound was telescoped to the next step – ^{1}H NMR was acquired to confirm the identity of this intermediate.

^{1}H NMR (400 MHz, $CDCl_3$): d 7.22 – 7.59 (m, 5H, 5 x ArH), 5.23 (br. s, 1H, OH), 4.20 (br. s, 1H, CH), 3.35 (s, 3H, CH_3), 2.19 (s, 3H, CH_3).

Consistent with reported data.[217]

Compound 37, 1-phenylprop-2-en-1-one

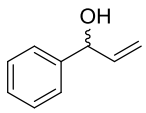


To a solution of 3-chloro-propiophenone (500 mg, 3 mmol, 1 eq.) in DCM (5 mL) at room temperature was added trimethylamine dropwise (830 µL, 7.6 mmol, 1 eq.). The reaction was stirred at room temperature for 2 h before being quenched with saturated NH_4Cl. The mixture was extracted with DCM, washed with 1 M HCl and dried with Na_2SO_4. Concentration *in vacuo* afforded the title compound as a yellow oil (392 mg, 99%). The compound was telescoped to the next step – ^{1}H NMR was acquired to confirm the identity of this intermediate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.90 (m, 2H, 2 x ArH), 7.61 – 7.53 (m, 1H, ArH), 7.51 – 7.45 (m, 2H, 2 x ArH), 7.15 (dd, 1H, CH, *J* = 17.1, 10.6 Hz), 6.43 (dd, 1H, CH, *J* = 17.1, 1.7 Hz), 5.93 (dd, 1H, CH, *J* = 10.6, 1.7 Hz).

Commercially available compound (CAS: 768-03-6), consistent with reported data[218]

Compound 39, 1-phenylprop-2-en-1-ol



To a solution of benzaldehyde (510 µL, 5 mmol, 1 eq.) in dry THF (20 mL) was added vinyl magnesium bromide (1 M in THF) (5.5 mL, 5.5 mmol, 1.1 eq.) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 hours. After this time, NH_4Cl (5 mL, aq, sat) and water (10 mL) were added and the mixture was extracted with ethyl acetate. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a clear, colourless oil (643 mg, 96 %).

υ_{max} (neat): 3334, 3080, 3025, 1490, 1451 cm^{-1}

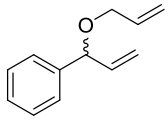
^1H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.27 (m, 5H, 5 x ArH), 6.13 – 6.03 (m, 1H, CH), 5.38 (d, *J* = 17.1 Hz, 1H), 5.25 – 5.19 (m, 2H), 2.27 (br. s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 139.8, 128.1, 127.3, 125.9, 114.6, 74.8.

HRMS ($C_9H_{14}ON$) $[M+NH_4]^+$ requires 152.1070, found 152.1068

Consistent with reported data.[219]

Compound 40, (1-(allyloxy)allyl)benzene



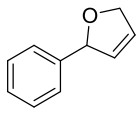
1-phenylprop-2-en-1-ol (268 mg, 2 mmol, 1 eq.) was dissolved in Et_2O (10 mL) and cooled to 0°C. KO*t*Bu (246 mg, 2.2 mmol, 1.1 eq.) was added slowly and the mixture was allowed to warm to room temperature over 30 minutes. After this time, the solution was again cooled to 0 °C and allyl bromide (190 µL, 2.2 mmol, 1.1 eq.) was added dropwise. The solution was allowed to warm to room temperature and stirred for 16 hours. Following this, water was added and the mixture was extracted with ethyl acetate. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (5% EtOAc/PE) to afford the title compound as a clear, yellow oil (240 mg, 69%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 4H, 4 x ArH), 7.34 – 7.27 (m, 1H, ArH), 6.05 – 5.90 (m, 2H, 2 x CH), 5.31 (dd, 2H, 2 x CH, *J* = 17.2, 4.6 Hz), 5.22 (t, 2H, 2 x CH, *J* = 9.3 Hz), 4.83 (d, 1H, CH, *J* = 6.6 Hz), 4.08 – 3.96 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.1, 139.0, 135.0, 128.6, 127.7, 127.0, 116.9, 116.3, 82.2, 69.3.

Consistent with reported data.[220]

Compound 41, 2-phenyl-2,5-dihydrofuran



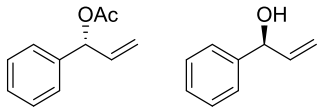
(1-(allyloxy)allyl)benzene (100 mg, 0.57 mmol, 1 eq.) was dissolved in DCM (8 mL) and Grubbs G2 catalyst (4.8 mg, 0.0057 mmol, 0.01 eq.) was added to the solution. After 30 minutes of stirring at room temperature, the solution was filtered through a pad of silica, rinsed with DCM and concentrated *in vacuo* to afford the title compound as a light brown oil (83 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H, 5 x ArH), 6.07 – 6.03 (m, 1H, CH), 5.94 – 5.89 (m, 1H, CH), 5.82 (ddd, 1H, CH, *J* = 7.9, 3.9, 1.9 Hz), 4.90 (dddd, 1H, CH, *J* = 12.8, 6.0, 2.3, 1.7 Hz), 4.79 (dddd, 1H, CH, *J* = 12.8, 4.1, 2.5, 1.6 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 130.1, 128.6, 127.9, 126.7, 126.5, 88.0, 75.9.

Consistent with reported data.[221]

Compound 42, (*R*)-1-phenylallyl acetate, Compound 38, (*S*)-1-phenylprop-2-en-1-ol



To a solution of 1-phenylprop-2-en-1-ol (268 mg, 2 mmol, 1 eq.) in toluene (20 mL) was added isopropyl acetate (469 µL, 8 mmol, 4eq.) and Novozyme (55 mg). The reaction was purged then stirred under an atmosphere of nitrogen at 40 °C for 16 h. The reaction mixture was filtered through a pad of silica, concentrated *in vacuo* then purified by flash chromatography (5% EtOAc/PE) to afford (*R*)-1-phenylallyl acetate as a white amorphous solid (144 mg, 41%, 96% ee by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H, 5 x ArH), 6.29 (d, 1H, CH, *J* = 5.9 Hz), 6.03 (ddd, 1H, CH, *J* = 16.7, 10.4, 5.9 Hz), 5.28 (dd, 2H, 2 x CH, *J* = 19.4, 13.8 Hz), 2.12 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 139.0, 136.4, 128.6, 128.3, 127.2, 117.0, 76.3, 21.3.

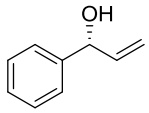
Consistent with reported data.[176]

Increasing the eluent to 50% EtOAc/PE afforded (*S*)-1-phenylprop-2-en-1-ol as a clear oil (39%, 105 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H, 5 x ArH), 6.10 (br. s, 1H, CH), 5.33 (d, *J* = 17.3 Hz, 1H), 5.25 – 5.21 (m, 2H), 2.24 (br. s, 1H, OH).

Consistent with the racemate data reported above (Compound 39).

Compound 43, (*R*)-1-phenylprop-2-en-1-ol

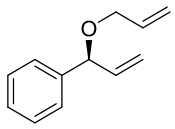


To a vial of (*R*)-1-phenylallyl acetate (100 mg, 0.57 mmol, 1 eq.) was added KOH (20 M, aq.) (1 mL, 20 mmol, 35 eq.) and the reaction was stirred for 3 h at 60 °C. The product was extracted with ethyl acetate, dried over Na_2SO_4 and concentrate *in vacuo* to afford the title compound (76 mg, 99%, 99% ee by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 4H, 4 x ArH), 7.32 – 7.28 (m, 1H, ArH), 6.08 (br. s, 1H, CH), 5.35 – 5.32 (m, 1H, CH), 5.25 – 5.22 (m, 2H), 2.20 (br. s, 1H, OH).

Consistent with the racemate data reported above (Compound 39).

Compound 44, (*S*)-(1-(allyloxy)allyl)benzene



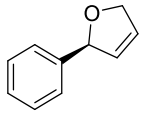
(*S*)-1-phenylprop-2-en-1-ol (268 mg, 2 mmol, 1 eq.) was dissolved in Et_2O (10 mL) and cooled to 0°C. KO*t*Bu (246 mg, 2.2 mmol, 1.1 eq.) was added slowly and the mixture was allowed to warm to room temperature over 30 minutes. After this time, the solution was again cooled to 0 °C and allyl bromide (190 µL, 2.2 mmol, 1.1 eq.) was added dropwise. The solution was allowed to warm to room temperature and stirred for 16 hours. Following this, water was added

and the mixture was extracted with ethyl acetate. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude material was purified by flash chromatography (5% EtOAc/PE) to afford the title compound as a yellow oil (209 mg, 69%, 95% ee by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.35 (m, 5H, 5 x ArH), 6.06 – 5.90 (m, 2H, 2 x CH), 5.33 – 5.30 m, 2H, 2 x CH), 5.25 (t, 2H, 2 x CH, *J* = 9.0 Hz), 4.84 – 4.82 (m, 1H, CH), 4.10 – 3.99 (m, 2H, 2 x CH).

Consistent with the racemate data reported above.

Compound 45, (*S*)-2-phenyl-2,5-dihydrofuran

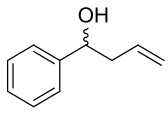


(*S*)-(1-(allyloxy)allyl)benzene (100 mg, 0.57 mmol, 1 eq.) was dissolved in DCM (8 mL) and Grubbs G2 catalyst (4.8 mg, 0.0057 mmol, 0.01 eq.) was added to the solution. After 30 minutes of stirring at room temperature, the solution was filtered through a pad of silica, rinsed with DCM and concentrated *in vacuo* to afford the title compound as a light brown oil (78 mg, 100%, 92% ee by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H, 5 x ArH), 6.07 – 6.03 (m, 1H, CH), 5.94 – 5.89 (m, 1H, CH), 5.82 (ddd, 1H, CH, *J* = 7.9, 3.9, 1.9 Hz), 4.90 (dddd, 1H, CH, *J* = 12.8, 6.0, 2.3, 1.7 Hz), 4.79 (dddd, 1H, CH, *J* = 12.8, 4.1, 2.5, 1.6 Hz).

Consistent with the racemate data reported above.

Compound 46, 1-phenylbut-3-en-1-ol



To a solution of benzaldehyde (510 µL, 5 mmol, 1 eq.) in dry THF (20 mL) was added allyl magnesium bromide (1 M in THF) (5.5 mL, 5.5 mmol, 1.1 eq.) dropwise at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 hours. After this time, NH_4Cl (5 ml, aq, sat) and water (10 ml) were added and the mixture was extracted with ethyl acetate.

The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a clear, colourless oil (688 mg, 93%).

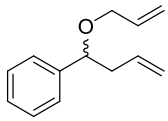
υ_{max} (neat): 3376, 3034, 2912, 1455 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 4H, 4 x ArH), 7.32 – 7.26 (m, 1H, ArH), 5.87 – 5.76 (m, 1H, CH), 5.20 – 5.12 (m, 2H, 2 x CH), 4.74 (dd, 1H, CH, *J* = 7.5, 5.4 Hz), 2.57 – 2.47 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 134.6, 128.6, 128.5, 128.5, 127.7, 126.0, 125.9, 118.5, 73.4, 43.9.

HRMS ($C_{10}H_{16}ON$) $[M+NH_4]^+$ requires 166.1226, found 166.1224

Compound 47, (1-(allyloxy)but-3-en-1-yl)benzene



1-Phenylbut-3-en-1-ol (296 mg, 2 mmol, 1 eq.) was dissolved in Et_2O (10 mL) and cooled to 0°C. KO*t*Bu (246 mg, 2.2 mmol, 1.1 eq.) was added slowly and the mixture was allowed to warm to room temperature over 30 minutes. After this time, the solution was again cooled to 0°C and allyl bromide (190 µL, 2.2 mmol, 1.1 eq.) was added dropwise. The solution was allowed to warm to room temperature and stirred for 16 hours. Following this, water was added and the mixture was extracted with ethyl acetate. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (5% EtOAc/PE) to afford the title compound as a clear, yellow oil (180 mg, 48%).

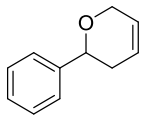
υ_{max} (neat): 3481, 3030, 2908, 2002, 1728 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 4H, 4 x ArH), 5.97 – 5.84 (m, 1H, ArH), 5.84 – 5.73 (m, 1H, CH), 5.29 – 5.21 (m, 1H, CH), 5.19 – 5.13 (m, 1H, CH), 5.10 – 4.99 (m, 2H, 2 x CH), 4.38 – 4.32 (m, 1H, CH), 3.94 (dd, 1H, CH, *J* = 12.8, 5.1 Hz), 3.78 (dd, 1H, CH, *J* = 12.8, 6.0 Hz), 2.66 – 2.57 (m, 1H, CH), 2.49 – 2.39 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 135.1, 135.0, 128.5, 127.7, 126.9, 117.0, 116.8, 81.3, 69.6, 42.7.

HRMS ($C_{13}H_{20}ON$) $[M+NH_4]^+$ requires 206.1539, found 206.1539

Compound 48, 2-phenyl-3,6-dihydro-2*H*-pyran



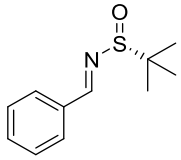
(1-(allyloxy)but-3-en-1-yl)benzene (100 mg, 0.53 mg, 1 eq.) was dissolved in DCM (8 mL) and Grubbs G2 catalyst (4.5 mg, 0.0053 mmol, 0.01 eq.) was added to the solution. After 30 minutes of stirring at room temperature, the solution was filtered through a pad of silica, rinsed with DCM and concentrated *in vacuo* to afford the title compound as a light brown oil (82 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.25 (m, 5H, 5 x ArH), 6.05 – 5.98 (m, 1H, alkene CH), 5.90 – 5.81 (m, 1H, alkene CH), 4.51 (dd, 1H, *J* = 10.0, 3.5 Hz), 4.40 – 4.19 (m, 2H, CH_2), 2.40 – 2.12 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.5, 128.2, 127.3, 126.2, 125.5, 124.4, 66.3, 32.8 (1C not observed).

Consistent with reported data.[222]

Compound 53, *N*-benzylidene-2-methylpropane-2-sulfinamide



To a flask containing benzaldehyde (1020 µL, 10 mmol, 1 eq.) and DCM (50 mL) was added (S)-*tert*-butanesulfinamide (1210 mg, 10 mmol, 1 eq.) and cesium carbonate (3.25 g, 10 mmol, 1 eq.). The reaction was stirred at room 40 °C for 16 h before being concentrated *in vacuo* and purified directly by flash chromatography (30% EtOAc/PE) to afford the title compound as a white amorphous solid (1944 mg, 93%).

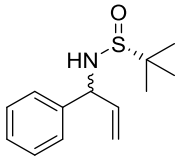
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1H, CH), 7.85 (d, 2H, 2 x ArH, *J* = 7.1 Hz), 7.56 – 7.44 (m, 3H, 3 x ArH), 1.27 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9, 134.3, 132.5, 129.5, 129.1, 57.9, 22.7.

HRMS ($C_{11}H_{16}NOS$) $[M+H]^+$ requires 210.0947, found 210.0944

Consistent with reported data.[223]

Compound 54, 2-methyl-*N*-(1-phenylallyl)propane-2-sulfinamide

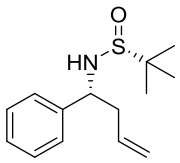


To a solution of N-benzylidene-2-methylpropane-2-sulfinamide (418 mg, 2 mmol, 1 eq.) in DCM (10 mL) at -78 °C, wad added vinyl magnesium bromide (1 M in THF) (2.2 mL, 2.2 mmol, 1.1 eq.) dropwise. The reaction was stirred at -78 °C for 4 h before being quenched with NH_4HCl then washed between water and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear oil. A ^{1}H NMR was taken to determine the diastereoselectivity of the reaction – comparison of the singlet peaks at 1.24 ppm and 1.20 ppm found the diastereomeric ratio to be 54:46.

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 4H, 4 x ArH), 7.30 – 7.26 (m, 1H, ArH), 6.04 (ddd, 1H, *J* = 17.1, 10.2, 6.9 Hz), 5.40 – 5.16 (m, 2H, 2 x CH), 5.00 – 4.91 (m, 1H, CH), 3.51 – 3.42 (m, 1H, CH), 1.24 (s, 9H, 3 x CH_3).

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 4H, 4 x ArH), 7.30 – 7.26 (m, 1H, ArH), 5.92 (ddd, 1H, *J* = 17.1, 10.2, 6.9 Hz), 5.40 – 5.16 (m, 2H, 2 x CH), 5.00 – 4.91 (m, 1H, CH), 3.51 – 3.42 (m, 1H, CH), 1.20 (s, 9H, 3 x CH_3).

Compound 55, 2-methyl-*N*-(1-phenylbut-3-en-1-yl)propane-2-sulfinamide



To a solution of *N*-benzylidene-2-methylpropane-2-sulfinamide (418 mg, 2 mmol, 1 eq.) in DCM (10 mL) at 0 °C, wad added allyl magnesium bromide (1 M in THF) (2.2 mL, 2.2 mmol, 1.1 eq.) dropwise. The reaction was stirred at -78 °C for 4 h before being quenched with

NH_4HCl then washed between water and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a slightly yellow clear oil (500 mg, 99%, >25:1 dr).

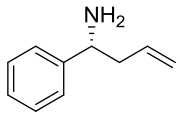
υ_{max} (neat): 3204, 3039, 2966, 1451, 1051 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 5H, 5 x ArH), 5.80 – 5.69 (m, 1H, CH), 5.21 – 5.14 (m, 2H, 2 x CH), 5.14 – 5.06 (m, 1H), 4.47 (ddd, 1H, CH, *J* = 8.0, 5.4, 2.3 Hz), 3.66 (s, 1H, NH), 2.64 – 2.57 (m, 1H, CH), 2.52 – 2.44 (m, 1H, CH), 1.19 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 134.1, 129.5, 129.0, 117.9, 58.6, 56.5, 41.6, 23.0.

HRMS ($C_{14}H_{22}NOS$) $[M+H]^+$ requires 252.1417, found 252.1416

Compound 56, (*R*)-1-phenylbut-3-en-1-amine



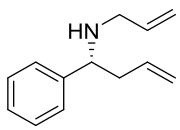
To a flask containing 2-methyl-N-(1-phenylbut-3-en-1-yl)propane-2-sulfinamide (251 mg, 1 mmol, 1 eq.) was added HCl/MeOH (10%) and the reaction was stirred for 16 h. Following this, the mixture was concentrated *in vacuo* and applied to an SCX column which had been rinsed with MeOH. The column was flushed with 2 column volumes of MeOH, then 2 column volumes of NH_3/MeOH. The resulting solution was concentrated *in vacuo* to afford the title compound as a yellow oil (91 mg, 62%, 98% ee by chiral HPLC).

^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H, 4 x ArH), 7.31 – 7.26 (m, 1H, ArH), 5.88 – 5.75 (m, 1H, CH), 5.21 – 5.12 (m, 2H, 2 x CH), 4.74 (dd, 1H, CH, *J* = 7.5, 5.4 Hz), 2.59 – 2.45 (m, 2H, 2 x CH), 2.14 (br. s, 1H, NH) (1H not observed, exchangeable).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.4, 135.9, 129.0, 127.6, 126.9, 118.5, 57.0, 46.0

Consistent with reported data.[224]

Compound 57, (*R*)-*N*-allyl-1-phenylbut-3-en-1-amine



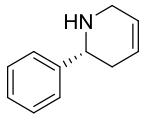
(*R*)-1-phenylbut-3-en-1-amine (100 mg, 0.68 mmol, 1 eq.) was dissolved in DMF (6 mL) and cooled to 0°C. NaH (18 mg, 0.75 mmol, 1.1 eq.) was added slowly and the mixture was allowed to warm to room temperature over 30 minutes. After this time, the solution was again cooled to 0 °C and allyl bromide (115 µL, 0.75 mmol, 1.1 eq.) was added dropwise. The solution was stirred at 40 °C for 48 hours. Following this, water was added and the mixture was extracted with ethyl acetate. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude material was purified by flash chromatography (24% EtOAc/PE) to afford the title compound as a light brown oil (70 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 4H, 4 x ArH), 7.19 – 7.15 (m, 1H, ArH), 5.84 – 5.74 (m, 1H, CH), 5.69 – 5.59 (m, 1H, CH), 5.10 – 4.94 (m, 4H, 4 x CH), 3.64 (t, 1H, CH, *J* = 6.8 Hz), 3.06 (dd, 1H, CH, *J* = 14.1, 5.4 Hz), 2.95 (dd, 1H, CH, *J* = 14.1, 6.7 Hz), 2.40 – 2.33 (m, 2H, 2 x CH), 1.66 (br. s, 1H, NH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 136.4, 135.6, 128.3, 127.4, 118.0, 116.0, 61.9, 50.3, 42.9.

Consistent with reported data.[225]

Compound 58, (*R*)-2-phenyl-1,2,3,6-tetrahydropyridine



To a flask containing crude (*R*)-*N*-allyl-2-methyl-*N*-(1-phenylbut-3-en-1-yl)propane-2-sulfonamide (40 mg, 0.13 mmol, 1 eq.) and Grubbs G2 (1.2 mg, 0.0027 mmol, 0.01 eq.) was added DCM. The reaction was stirred at room temperature for 2 h before being filtered through a pad of silica. The solution was concentrated *in vacuo*, HCl/MeOH (10%) was added and the reaction was stirred for 16 h. Following this, the mixture was concentrated *in vacuo* and applied to an SCX column which had been rinsed with MeOH. The column was flushed with 2 column volumes of MeOH, then 2 column volumes of NH_3/MeOH. The resulting solution was concentrated *in vacuo* to afford the title compound as a yellow oil (4 mg, 13% over three steps).

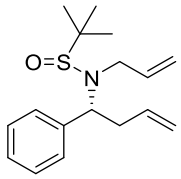
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, 2H, 2 x ArH, *J* = 7.4 Hz), 7.29 – 7.24 (m, 3H, 3 x ArH), 5.63 (ddt, 1H, 1 x CH, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.19 – 5.11 (m, 2H, 2 x CH), 4.68 – 4.61

(m, 1H, CH), 4.30 (d, 1H, CH, *J* = 8.8 Hz), 2.61 (t, 2H, 2 x CH, *J* = 6.8 Hz) (1H missing, exchangeable).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.1, 129.8, 127.4, 126.0, 120.0, 57.6, 43.5, 29.5 (1C not observed).

Consistent with reported data.[226]

Compound 59, *N*-allyl-2-methyl-N-((*R*)-1-phenylbut-3-en-1-yl)propane-2-sulfinamide



2-methyl-*N*-(1-phenylbut-3-en-1-yl)propane-2-sulfinamide (61 mg, 0.2 mmol, 1 eq.) was dissolved in DMF (2 mL) and cooled to 0 °C. NaH (5 mg, 0.22 mmol, 1.1 eq.) was added slowly and the mixture was allowed to warm to room temperature over 30 minutes. After this time, the solution was again cooled to 0 °C and allyl bromide (34 µL, 0.22 mmol, 1.1 eq.) was added dropwise. The solution was allowed to warm and stirred at 40 °C for 28 hours. Following this, aqueous LiCl (10 ml) was added and the mixture was extracted with ethyl acetate (3 x 20 ml). The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude material was purified by flash chromatography (50%) to afford the title compound as a clear, yellow oil (41 mg, 67%). NMR showed slight impurity so compound was telescoped to the next reaction. ^{1}H NMR of product peaks is detailed below.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, 2H, 2 x ArH, *J* = 7.8 Hz), 7.27 (t, 2H, 2 x ArH, *J* = 6.8 Hz), 7.24 – 7.18 (m, 1H, ArH), 5.69 – 5.61 (m, 1H, CH), 5.55 – 5.44 (m, 1H, CH), 5.13 – 5.07 (m, 2H, 2 x CH), 5.00 – 4.81 (m, 2H, 2 x CH), 4.14 – 4.07 (m, 1H, CH), 3.81 (d, 1H, CH, *J* = 16.8 Hz), 2.92 (dd, 1H, CH, *J* = 16.9, 6.7 Hz), 2.88 – 2.79 (m, 1H, CH), 2.67 – 2.59 (m, 1H, CH), 1.18 (s, 9H, 3 x CH_3).

Compound 62, tetrahydrofuran-3-ol

To a flask containing 2,5-dihydrofuran (378 µL, 5 mmol, 1 eq.) in THF (20 mL) under nitrogen was added BH_3.THF (1 M in THF) (5.5 mL, 5.5 mmol, 1.1 eq.) at 0 °C. The solution was

allowed to warm to room temperature then stirred at room temperature for 16 h. Following this, the reaction was cooled to 0 °C and NaOH (1 g, 25 mmol, 5 eq.) and H_2O_2 (30% in water, 4 mL, 50 mmol, 10 eq.) were added. The reaction was washed between Et_2O and sodium metabisulfite (aq.) solution. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear oil (286 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.43 – 4.31 (m, 1H, CH), 3.11 (dt, 1H, CH, *J* = 11.0, 7.5 Hz), 2.89 (d, 1H, CH, *J* = 11.9 Hz), 2.86 – 2.78 (m, 2H, 2 x CH), 2.60 (br. s, 1H, OH), 1.99 – 1.88 (m, 1H, CH), 1.76 – 1.65 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 75.1, 71.5, 66.5, 36.0

Commercially available compound (CAS: 453-20-3), consistent with reported data[227]

Compound 63, dihydrofuran-3(2*H*)-one

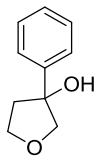
To a flask containing tetrahydrofuran-3-ol (200 mg, 2.27 mmol, 1 eq.) in DCM (5 mL) was added PCC (736 mg, 3.4 mmol, 1.5 eq.) at 0 °C. The reaction was then allowed to warm to room temperature, Celite (~200 mg) was added and the reaction was stirred for 16 h. Following this, filtration through a pad of silica afforded crude material which was concentrated *in vacuo* and purified by flash chromatography (20% Et_2O/PE) to afford the title compound as a white amorphous solid (107 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (t, *J* = 7.3 Hz, 2H), 3.88 (s, 2H), 2.51 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.9, 70.1, 66.3, 36.5

Commercially available compound (CAS: 22929-52-8), consistent with reported data.

Compound 64, 3-phenyltetrahydrofuran-3-ol



To a solution of dihydrofuran-3(2*H*)-one (300 mg, 3.5 mmol, 1 eq.) in THF (10 mL) was added phenyl magnesium bromide (3 M in THF) (1.3 mL, 3.85, 1.1 eq.) at 0 ^{0}C. The reaction was allowed to warm to room temperature then stirred for 16 h. Following this, NH_4Cl (aq. sat.) was added and the mixture was washed between ethyl acetate and brine. The organic layer was dried with Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (30% EtOAc/PE) to afford the title compound as an off-white amorphous solid (528 mg, 92%).

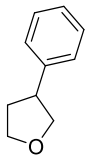
υ_{max} (neat): 3301, 3055, 2935, 1523, 1421 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dq, *J* = 2.7, 1.8 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.35 – 7.30 (m, 1H), 4.29 – 4.20 (m, 1H), 4.15 (td, *J* = 8.8, 3.5 Hz, 1H), 4.02 (dd, *J* = 9.4, 1.3 Hz, 1H), 3.94 (d, *J* = 9.4 Hz, 1H), 2.46 (dt, *J* = 13.0, 9.1 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.27 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.9, 128.0, 127.0, 124.9, 81.3, 79.8, 67.5, 41.3.

HRMS ($C_{10}H_{12}O_2$) $[M+H]^+$ requires: 220.0968, found $[M+H]^+$ 220.0968

Compound 65, 3-phenyltetrahydrofuran



To a flask containing Pd/C (164 mg, 0.1 mmol, 0.05 eq.) under nitrogen was added a solution of 3-phenyltetrahydrofuran-3-ol (328 mg, 2 mmol, 1 eq.) in ethanol (5 mL). The flask was purged with H_2, and then stirred under an atmosphere of H_2 for 16 h at room temperature. The reaction mixture was filtered through Celite, rinsed with ethyl acetate and concentrated *in vacuo* to afford a clear oil. The crude material was purified by flash chromatography (5% EtOAc/PE) to afford the title compound as a clear oil (251 mg, 83%).

υ_{max} (neat): 3001, 2934, 1610, 1499 cm^{-1}

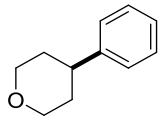
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 5H), 4.18 (t, 1H), 4.10 (td, *J* = 8.3, 4.5 Hz, 1H), 3.95 (td, *J* = 8.1, 7.3 Hz, 1H), 3.76 (t, 1H), 3.43 (quin., *J* = 7.9 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.04 (dq, *J* = 12.3, 8.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.5, 128.6, 127.0, 125.9, 74.8, 67.9, 45.9, 34.3.

HRMS ($C_{10}H_{13}O$) $[M+H]^+$ requires: 149.0958, found $[M+H^+]$ 149.0961

Consistent with reported data.[228]

Compound 74, 4-phenyltetrahydro-2*H*-pyran



Synthesised according to General Procedure I using bromobenzene (26 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL). The crude material was taken up in DCM and washed with water (3 x 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear, colourless oil (38.3 mg, 95%).

Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL). The crude material was taken up in DCM and washed with water (3 x 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear, colourless oil (38 mg, 94%).

υ_{max} (neat): 2923, 2844, 1555 cm^{-1}

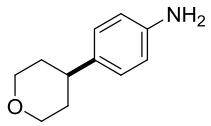
^1H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 2H, 2 x ArH), 7.25 – 7.19 (m, 3H, 2 x ArH), 4.10 – 4.07 (m, 2H, 2 x CH), 3.54 (td, 2H, 2 x CH, *J* = 11.6, 2.4 Hz), 2.76 (tt, 1H, CH, *J* = 11.7, 4.2 Hz), 1.88 – 1.74 (m, 4H, 2 x CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.0, 128.7, 126.9, 126.5, 68.6, 41.7, 34.1.

HRMS ($C_{11}H_{15}O$) $[M+H]^+$ requires: 163.1115, observed: 163.1117

Consistent with reported data.[229]

Compound 75, 4-(tetrahydro-2*H*-pyran-4-yl)aniline



Synthesised according to General Procedure I using 1-bromo-4-nitrobenzene (51 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL) and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a pale yellow amorphous solid (38.4 mg, 88%).

Synthesised according to General Procedure L using 1-bromo-4-nitrobenzene (51 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL) and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a pale yellow amorphous solid (38 mg, 87%).

Synthesised according to General Procedure L using *N*-Cbz-bromoaniline (76 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (2 mL) and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a pale yellow amorphous solid (24 mg, 54%).

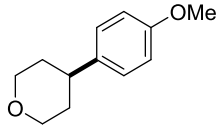
υ_{max} (neat): 3390, 3313, 3067, 2993, 2961, 2806, 1645, 1501 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 6.65 (d, 2H, 2 x ArH, *J* = 8.4 Hz), 4.07 – 4.05 (m, 2H, 2 x CH), 3.51 (td, 2H, 2 x CH, *J* = 11.4, 3.0 Hz), 3.39 (br. s, 2H, NH_2), 2.68 – 2.60 (m, 1H, CH), 1.81 – 1.71 (m, 4H, 2 x CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 144.8, 136.3, 127.6, 115.4, 68.6, 40.8, 34.4.

HRMS ($C_{11}H_{16}ON$) $[M+H]^+$ requires: 178.1224, observed: 178.1226

Compound 77, 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran



Synthesised according to General Procedure I using 4-bromoanisole (31 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and

MeOH (2 mL), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound a colourless oil (34 mg, 70%).

Synthesised according to General Procedure L using 4-bromoanisole (31 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (2 mL), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound a colourless oil (34 mg, 70%).

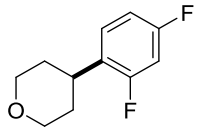
υ_{max} (neat): 2932, 2833, 1703, 1677, 1610, 1513 cm^{-1}

^{1}H NMR (500 MHz, MeOD): δ 7.14 (d, 2H, 2 x ArH, *J* = 8.6 Hz), 6.84 (d, 2H, 2 x ArH, *J* = 8.7 Hz), 4.04 – 3.99 (m, 2H, 2 x CH), 3.76 (s, 3H, CH_3), 3.55 – 3.51 (m, 2H, 2 x CH), 2.75 – 2.67 (m, 1H, CH), 1.78 – 1.71 (m, 4H, 2 x CH_2).

^{13}C NMR (101 MHz, MeOD): δ 159.6, 139.4, 128.6, 114.9, 69.5, 55.6, 41.8, 35.4.

HRMS ($C_{12}H_{16}O_2$) [M] requires: 192.1150, observed: 192.1142

Compound 79, 4-(2,4-difluorophenyl)tetrahydro-2*H*-pyran



Synthesised according to General Procedure L using 1-bromo-2,4-difluorobenzene (28 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (2 mL), and purified by flash column chromatography (8% EtOAc/PE) to afford the title compound a clear, colourless oil (31 mg, 62%).

υ_{max} (neat): 3083, 2924, 2848, 1617, 1606, 1506 cm^{-1}

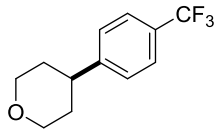
^{1}H NMR (400 MHz, MeOD) δ 7.37 – 7.31 (m, 1H, ArH), 6.97 – 6.87 (m, 2H, 2 x ArH), 4.09 – 4.02 (m, 2H, 2 x CH), 3.59 (td, 2H, 2 x CH, *J* = 11.8, 2.2 Hz), 3.12 (tt, 1H, CH, *J* = 12.0, 3.8 Hz), 1.90 – 1.82 (m, 2H, 2 x CH), 1.77 – 1.70 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, (dd, $^1J_{C\text{-}F}$ 235.3 Hz, $^2J_{C\text{-}F}$ = 12.2 Hz,), 160.0, (dd, $^3J_{C\text{-}F}$ = 237.4 Hz, $^2J_{C\text{-}F}$ = 11.,) 128.5 (m) 128.3 (m) 111.29 (dd, $^2J_{C\text{-}F}$ = 20.5, $^3J_{C\text{-}F}$ = 3.5 Hz), 103.9 (t, $^2J_{C\text{-}F}$ = 26.1 Hz), 68.4, 34.2, 32.8.

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.61, -115.49.

HRMS ($C_{11}H_{13}OF_2$) $[M+H]^+$ requires: 198.0856, observed: 198.0853

Compound 83, 4-(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran



Synthesised according to General Procedure L using 4-trifluorobromobenzene (35 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL). The crude material was taken up in DCM and washed with water (3 x 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (55 mg, 95%).

Synthesised according to General Procedure L using 4-trifluorobromobenzene (35 µL, 0.25 mmol 1 equiv.) and potassium 3,6-dihydro-2*H*-pyran-4-trifluoroborate (48 mg, 0.25 mmol, 1 equiv.) and MeOH (1 mL). The crude material was taken up in DCM and washed with water (3 x 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (53 mg, 92%).

υ_{max} (neat): 2934, 2842, 1719, 1619 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, 2H, 2 x ArH, *J* = 8.1 Hz), 7.34 (d, 2H, 2 x ArH, *J* = 8.1 Hz), 4.10 (dd, 2H, 2 x CH, *J* = 11.2, 4.0 Hz), 3.54 (td, 2H, 2 x CH, *J* = 11.6, 2.4 Hz), 2.87 – 2.78 (m, 1H, CH), 1.88 – 1.75 (m, 4H, 2 x CH_2).

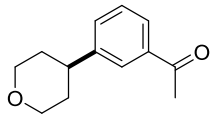
^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 128.7 (q, $^2J_{C\text{-}F}$ 32.3 Hz), 127.3, 125.7 (q, $^3J_{C\text{-}F}$ = 4.1 Hz), 123.1, 68.3, 41.7, 33.8.

^{19}F NMR (471 MHz, $CDCl_3$): -62.39.

HRMS ($C_{12}H_{14}OF_3$) $[M+H]^+$ requires: 231.0992, observed: 231.0991

Consistent with reported data.[230]

Compound 76, 1-(3-(tetrahydro-2*H*-pyran-4-yl)phenyl)ethan-1-one



Synthesised according to General Procedure L using 3-bromoacetophenone (33 μL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL), and purified by flash column chromatography (12% EtOAc/PE) to afford the title compound as a clear, colourless oil (48 mg, 94%).

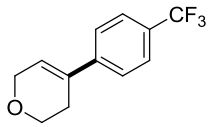
υ_{max} (neat): 2915, 2839, 1680 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H, ArH), 7.80 (dt, 1H, ArH, *J* = 6.9, 1.8 Hz), 7.46 – 7.39 (m, 2H, 2 x ArH), 4.09 (dd, 2H, 2 x CH, *J* = 11.1, 4.0 Hz), 3.54 (td, 2H, 2 x CH, *J* = 11.6, 2.4 Hz), 2.87 – 2.79 (m, 1H, CH), 2.61 (s, 3H, CH_3), 1.89 – 1.75 (m, 4H, 2 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.4, 146.5, 137.6, 131.7, 128.9, 126.7, 126.7, 68.4, 41.6, 33.9, 26.8.

HRMS ($C_{13}H_{17}O_2$) $[M+H]^+$ requires: 205.1221, observed: 205.1223

Compound 89, 4-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2*H*-pyran



To an oven dried 2-5 mL μW vial was added 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.), 4-trifluorobromobenzene (35 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2.DCM, and K_2CO_3 (104 mg, 0.75 mmol, 3 eq.). The vial was capped and purged, then 1,4-dioxane (950 μL) and water (50 μL) were added. The reaction mixture was stirred at 80 °C for 4 h then was allowed to cool to room temperature and the vial was decapped. The reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with ethyl acetate. The solvent was removed *in vacuo* and the crude material was purified by flash

column chromatography (5% EtOAc/PE) to afford the title compound as an off-white solid (54 mg, 95%).

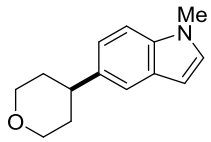
υ_{max} (neat): 2918, 2809, 1586, 1452 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.49 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 6.22 (s, 1H, CH), 4.35 (d, 2H, 2 x CH, *J* = 2.7 Hz), 3.95 (t, 2H, 2 x CH, *J* = 5.4 Hz), 2.53 (dd, 2H, 2 x CH, *J* = 4.4, 2.5 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.8, 133.4, 129.0 (q, *J* = 32.2 Hz), 125.6, 125.1, 124.9, 123.0, 65.9, 64.4, 27.2.

HRMS ($C_{12}H_{12}OF_3$) $[M+H]^+$ requires: 229.0833, observed: 229.0835

Compound 92, 1-methyl-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indole



Synthesised according to General Procedure L using 5-bromo-1-methylindole (53 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound as a pale yellow amorphous solid (30 mg, 56%).

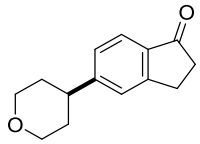
υ_{max} (neat): 2922, 2850, 1736, 1591 cm^{-1}

^1H NMR (500 MHz, MeOD): δ 7.39 (s, 1H, ArH, *J* = 0.7 Hz), 7.28 (d, 1H, ArH, *J* = 8.5 Hz), 7.09 (d, 1H, ArH, *J* = 3.1 Hz), 7.07 (dd, 1H, ArH, *J* = 8.5, 1.5 Hz), 6.36 (d, 1H, ArH, *J* = 2.7 Hz), 4.04 (dd, 2H, 2 x CH, *J* = 10.9, 3.9 Hz), 3.76 (s, 3H, CH_3), 3.58 (td, 2H, 2 x CH, *J* = 11.6, 2.4 Hz), 2.87 – 2.81 (m, 1H, CH), 1.89 – 1.75 (m, 4H, 2 x CH_2).

^{13}C NMR (101 MHz, MeOD): δ 137.9, 137.2, 130.3, 119.0 121.7, 110.1, 101.5, 69.7, 42.8, 36.0, 32.8 (1C not observed).

HRMS ($C_{14}H_{18}ON$) $[M+H]^+$ requires: 216.1385, observed: 216.1383

Compound 93, 5-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-amine



Synthesised according to General Procedure L using 5-bromo-1-indanone (53 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL), and purified by flash column chromatography (25% EtOAc/PE) to afford the title compound an off-white amorphous solid (28 mg, 52%).

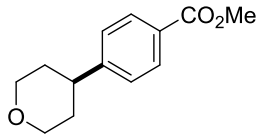
υ_{max} (neat): 2949, 2930, 2846, 1701, 1610 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 1H, ArH, *J* = 8.2 Hz), 7.34 – 7.31 (m, 1H, ArH), 7.24 (ddd, 1H, ArH, *J* = 7.9, 1.4, 0.6 Hz), 4.12 – 4.07 (m, 2H, 2 x CH), 3.54 (td, 2H, 2 x CH, *J* = 11.7, 2.4 Hz), 3.14 – 3.10 (m, 2H, CH_2), 2.85 (tt, 1H, CH, *J* = 11.8, 4.1 Hz), 2.70 – 2.66 (m, 2H, 2 x CH), 1.89 – 1.75 (m, 4H, 2 x CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.6, 156.0, 153.4, 135.8, 126.7, 124.8, 124.0, 68.3, 42.3, 36.6, 33.8, 25.9.

HRMS ($C_{14}H_{17}O_2$) $[M+H]^+$ requires: 217.1229, observed: 217.1233

Compound 94, methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate



Synthesised according to General Procedure L using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL) and purified by flash column chromatography (25% EtOAc/PE) to afford the title compound as an off-white amorphous solid (32 mg, 59%).

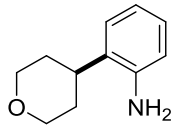
υ_{max} (neat): 3099, 2983, 2799, 1744 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.29 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 4.09 (dd, 2H, 2 x CH, *J* = 11.2, 3.9 Hz), 3.90 (s, 3H, CH_3), 3.53 (td, 2H, 2 x CH, *J* = 11.6, 2.3 Hz), 2.82 (tt, 1H, CH, *J* = 11.7, 4.1 Hz), 1.87 – 1.85 (m, 4H, 2 x CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.1, 151.2, 130.0, 128.4, 126.9, 68.3, 52.1, 41.8, 33.7.

HRMS ($C_{13}H_{16}O_3Na$) $[M+Na]^+$ requires: 243.0993, observed: 243.0992

Compound 95, 2-(tetrahydro-2*H*-pyran-4-yl)aniline



Synthesised according to General Procedure L using 1-bromo-2-nitrobenzene (51 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL) and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a pale yellow amorphous solid (30 mg, 68%).

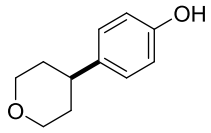
υ_{max} (neat): 3393, 3333, 3009, 2937, 2841, 1634, 1615, 1521 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, 1H, ArH *J* = 7.7, 1.4 Hz), 7.05 (td, 1H, ArH, *J* = 7.7, 1.5 Hz), 6.81 (td, 1H, ArH, *J* = 7.6, 0.9 Hz), 6.71 (dd, 1H, ArH, *J* = 7.9, 1.0 Hz), 4.16 – 4.07 (m, 2H, 2 x CH), 3.57 (td, 2H, 2 x CH, *J* = 11.4, 3.2 Hz), 2.81 – 2.69 (m, 1H, CH), 1.90 – 1.74 (m, 4H, 2 x CH_2), 2H not observed (exchangeable).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.5, 129.9, 127.1, 126.3, 119.5, 116.3, 68.8, 36.0, 32.5.

HRMS ($C_{11}H_{16}ON$) $[M+H]^+$ requires: 178.1224, observed: 178.1226

Compound 75, 4-(tetrahydro-2*H*-pyran-4-yl)phenol



Synthesised according to General Procedure L using 4-benzyloxybromobenzene (66 mg, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (2 mL), and purified by flash column chromatography (60% EtOAc/PE) to afford the title compound an off-white amorphous solid (34 mg, 76%).

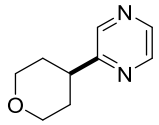
υ_{max} (neat): 3290, 2986, 1703, 1673 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, 2H, 2 x ArH, *J* = 8.4 Hz), 6.78 (d, 2H, 2 x ArH, *J* = 8.5 Hz), 4.91 (s, 1H, OH), 4.09 – 4.06 (ddd, 2H, 2 x CH, *J* = 15.8, 10.6, 4.8 Hz), 3.55 – 3.50 (td, 2H, 2 x CH, *J* = 11.3, 3.1 Hz), 2.72 – 2.66 (m, 1H, CH), 1.83 – 1.71 (m, 4H, 2 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 138.3, 128.0, 115.4, 68.6, 40.8, 34.3.

HRMS ($C_{11}H_{15}O_2$) $[M+H]^+$ requires: 179.1069, observed 179.1072

Compound 98, 2-(tetrahydro-2*H*-pyran-4-yl)pyrazine



Synthesised according to General Procedure L using chloropyrazine (22 µL, 0.25 mmol, 1 equiv.), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and MeOH (1 mL), and purified by flash column chromatography (35% EtOAc/PE) to afford the title compound as a yellow oil (39 mg, 96%).

υ_{max} (neat): 3433, 3055, 2950, 2922, 2848, 1729, 1651, 1470 cm^{-1}

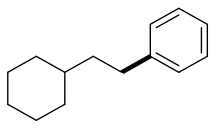
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (br, s, 2H, 2 x ArH, *J* = 24.2 Hz), 8.41 (br. s, 1H, ArH), 4.08 (dd, 2H, 2 x CH, *J* = 11.1, 3.9 Hz), 3.53 (td, 2H, 2 x CH, *J* = 11.8, 2.1 Hz), 2.98 (tt, 1H, CH, *J* = 11.8, 3.9 Hz), 1.93 (ddd, 2H, 2 x CH, *J* = 16.3, 12.6, 4.4 Hz), 1.83 (dd, 2H, 2 x CH, *J* = 13.1, 1.8 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7, 144.2, 143.4, 142.7, 67.9, 41.1, 31.9.

HRMS ($C_9H_{13}ON_2$) $[M+H]^+$ requires: 165.1020, observed: 165.1022

Consistent with reported data.[231]

Compound 99, (2-cyclohexylethyl)benzene



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.), (2- 2-[(1*E*)-2-(1-cyclohexen-1-yl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound a colourless oil (37 mg, 79%).

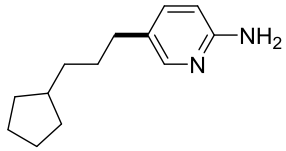
υ_{max} (neat): 3027, 2921, 2852, 2325, 1498, 1450 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 2H, 2 x ArH), 7.20 – 7.14 (m, 3H, 3 x ArH), 2.65 – 2.58 (m, 2H, CH_2), 1.81 – 1.68 (m, 4H, 4 x CH), 1.53 – 1.47 (m, 2H, 2 x CH), 1.33 – 1.13 (m, 5H, 5 x CH), 0.94 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4, 128.5, 128.4, 125.6, 39.6, 37.5, 33.5, 33.4, 26.9, 26.5.

HRMS ($C_{14}H_{20}$) [M] requires: 188.1565, observed: 188.1571

Compound 100, 5-(3-cyclopentylpropyl)pyridin-2-amine



Synthesised according to General Procedure L using 5-bromo-2-nitropyridine (51 mg, 0.25 mmol, 1 equiv.) and 2-(2-cyclopentylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (51 mg, 0.25 mmol, 1 equiv.). The filtrate was concentrated *in vacuo*, extracted with DCM and washed with water (3x). The solvent was removed *in vacuo* to afford the title compound without further purification as a yellow amorphous solid (47 mg, 99%).

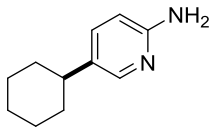
υ_{max} (neat): 3462, 3306, 3168, 3014, 2943, 2921, 2855, 1623, 1504, 1405 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, 1H, ArH, J = 2.1 Hz), 7.24 (dd, 1H, ArH, J = 8.3, 2.2 Hz), 6.43 (d, 1H, ArH, J = 8.3 Hz), 4.34 (br. s, 2H, NH_2), 2.43 (t, 2H, CH_2, J = 7.6 Hz), 1.74 – 1.71 (m, 3H), 1.57 – 1.47 (m, 6H), 1.35 – 1.24 (m, 2H), 1.12 – 0.93 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 147.5, 138.1, 128.1, 108.5, 40.1, 35.7, 32.8, 32.5, 30.7, 25.3

HRMS ($C_{13}H_{21}N_2$) $[M+H]^+$ requires: 205.1695, observed: 205.1699

Compound 101, 5-cyclohexylpyridin-2-amine



Synthesised according to General Procedure L using 5-bromo-2-nitropyridine (51 mg, 0.25 mmol, 1 equiv.) and 1-cyclohexen-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (80% PE/EtOAc) to afford the title compound an off-white solid (24 mg, 54%).

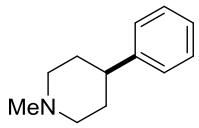
υ_{max} (neat): 3441, 3304, 3144, 2918, 2847, 1639, 1505 cm^{-1}

^{1}H NMR (600 MHz, acetone-d_6) δ 7.82 (d, 1H, ArH, *J* = 1.8 Hz), 7.27 (dd, 1H, ArH, *J* = 8.4, 2.3 Hz), 6.47 (d, 1H, ArH, *J* = 8.4 Hz), 5.11 (br. s, 2H, NH_2), 2.40 – 2.33 (m, 1H, CH), 1.84 – 1.74 (m, 4H, 4 x CH), 1.74 – 1.68 (m, 1H, CH), 1.41 – 1.35 (m, 4H, 4 x CH), 1.28 – 1.22 (m, 1H, CH).

^{13}C NMR (151 MHz, acetone-d_6): δ 159.1, 147.0, 136.4, 132.5, 108.7, 42.0, 35.3, 27.6, 26.7.

HRMS ($C_{11}H_{17}N_2$) $[M+H]^+$ requires: 177.1383, observed: 177.1386

Compound 102, 1-methyl-4-phenylpiperidine



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (56 mg, 0.25 mmol, 1 equiv.). The crude material was dissolved in minimal MeOH and applied to a 1g SCX cartridge which had been equilibrated with MeOH. The cartridge was washed with 2 column volumes of MeOH, followed by 2 column volumes of NH_3/MeOH (3 M). The NH_3/MeOH fractions were combined and concentrated *in vacuo* to afford the title compound as a yellow oil (30 mg, 68%).

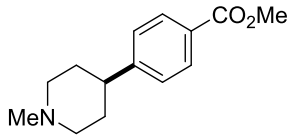
υ_{max} (neat): 3062, 3030, 2975, 2934, 2848, 2779, 1645, 1446, 1454 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H, 2 x ArH), 7.25 – 7.17 (m, 3H, 3 x ArH), 2.97 (d, 2H, 2 x CH, *J* = 11.5 Hz), 2.50 – 2.42 (m, 1H, CH), 2.32 (s, 3H, CH_3), 2.05 (td, 2H, 2 x CH, *J* = 11.2, 4.2 Hz), 1.87 – 1.75 (m, 4H, 2 x CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 128.6, 127.0, 126.3, 56.5, 46.6, 42.2, 33.6.

HRMS ($C_{12}H_{16}N$) $[M-H]^-$ requires: 174.1276, observed: 174.1277

Compound 103, methyl 4-(1-methylpiperidin-4-yl)benzoate



Synthesised according to General Procedure L using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (56 mg, 0.25 mmol, 1 equiv.). The crude material was dissolved in minimal MeOH and applied to a 1g SCX cartridge which had been equilibrated with MeOH. The cartridge was washed with 2 column volumes of MeOH, followed by 2 column volumes of NH_3/MeOH (3 M). The NH_3/MeOH fractions were combined and concentrated *in vacuo* to afford the title compound as a yellow oil (58 mg, 99%).

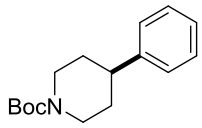
υ_{max} (neat): 3034, 2937, 2844, 2781, 2738, 1722, 1612 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 2H, 2 x ArH, *J* = 8.4 Hz), 7.28 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 3.89 (s, 3H, CH_3), 3.00 (d, 2H, 2 x CH, *J* = 11.8 Hz), 2.60 – 2.48 (m, 1H, CH), 2.33 (s, 3H, CH_3), 2.13 – 2.02 (m, 2H, 2 x CH), 1.87 – 1.78 (m, 4H, 2 x CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.2, 151.7, 129.9, 128.3, 127.0, 56.2, 52.1, 46.4, 42.2, 33.2.

HRMS ($C_{14}H_{20}O_2N$) $[M+H]^+$ requires: 234.1485, observed: 234.1489

Compound 104, *tert*-butyl 4-phenylpiperidine-1-carboxylate



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound as a yellow oil (43 mg, 66%).

Synthesised according to General Procedure W using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound as a yellow oil (61.3 mg, 94%).

υ_{max} (neat): 2945, 2843, 1667, cm^{-1}

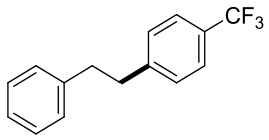
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 2H, 2 x ArH), 7.24 – 7.18 (m, 3H, 3 x ArH), 4.24 (br. s, 2H, CH_2), 2.80 (t, 2H, *J* = 12.4 Hz, 2 x CH), 2.64 (tt, 1H, CH, *J* = 12.2, 3.6 Hz), 1.83 (d, 2H, 2 x CH, *J* = 13.3 Hz), 1.63 (qd, 2H, 2 x CH, *J* = 12.8, 4.3 Hz), 1.49 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 145.9, 128.6, 126.9, 126.5, 79.5, 44.6, 42.9, 33.3, 28.6.

HRMS ($C_{16}H_{23}O_2NNa$) $[M+Na]^+$ requires: 284.1621, observed: 284.1621

Consistent with reported data.[232]

Compound 105, 1-phenethyl-4-(trifluoromethyl)benzene



Synthesised according to General Procedure L using 4-bromobenzotrifluoride (35 µL, 0.25 mmol, 1 equiv.) and *trans*-2-Phenylvinylboronic acid pinacol ester (58 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (1% EtOAc/PE) to afford the title compound a colourless oil (58 mg, 93%).

υ_{max} (neat): 2926, 2856, 1595, 1449cm^{-1}

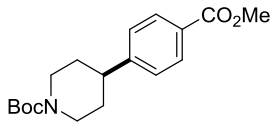
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, 2H, 2 x ArH, *J* = 8.0 Hz), 7.28 – 7.26 (m, 4H, 4 x ArH), 7.23 – 7.20 (m, 1H, 1 x ArH), 7.17 (d, 2H, 2 x ArH, *J* = 7.1 Hz), 3.02 – 2.97 (m, 2H, CH_2), 2.97 – 2.92 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 141.2, 128.9, 128.6, 126.3, 125.4 (q, *J* = 3.3 Hz) 123.2, 37.8, 37.7 (2C not observed).

^{19}F NMR: (376 MHz, $CDCl_3$) δ -62.29.

HRMS ($C_{15}H_{13}F_3$) [M] requires: 250.0969, observed: 250.0975

Compound 106, *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



Synthesised according to General Procedure L using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (50% EtOAc/PE) to afford the title compound as a yellow oil (59 mg, 71%).

Synthesised according to General Procedure W using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.). The crude material was taken up in ethyl acetate and washed with water (2 x 10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white amorphous solid (79.6 mg, 99%).

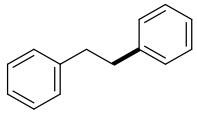
υ_{max} (neat): 2974, 2928, 2849, 1686 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.26 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 4.25 (br. s, 2H, 2 x CH), 3.89 (s, 3H, CH_3), 2.80 (t, 2H, 2 x CH, *J* = 11.0 Hz), 2.70 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.82 (d, 2H, *J* = 13.0 Hz, 2 x CH), 1.62 (qd, 2H, 2 x CH, *J* = 12.7, 4.3 Hz), 1.47 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 154.9, 151.2, 130.0, 128.5, 127.0, 79.7, 52.1, 44.3, 42.9, 33.0, 28.6

HRMS ($C_{16}H_{26}O4$ N) $[M+H]^+$ requires: 320.1856, observed: 320.1856

Compound 107, 1,2-diphenylethane



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and 2-phenylvinylboronic acid (37 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound as a colourless oil (42 mg, 90%).

Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and trans-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styrene (58 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound as a colourless oil (41 mg, 87%).

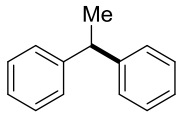
υ_{max} (neat): 3027, 2928, 2915, 1496, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H), 7.23 – 7.18 (m, 6H), 2.94 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 128.6, 128.5, 126.1, 38.1.

HRMS ($C_{14}H_{14}$) [M] requires: 182.1095, observed: 182.1092

Compound 108, ethane-1,1-diyldibenzene



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and 2-phenylvinylboronic acid (37 mg, 0.25 mmol, 1 equiv. (37 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound as a colourless oil (30 mg, 65%).

Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (58 mg, 0.25 mmol, 1 equiv. (37 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound as a colourless oil (39 mg, 86%).

Synthesised according to General Procedure L using α-bromostyrene (36 µL, 0.25 mmol, 1 equiv.) and phenyl boronic acid (31 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (100% PE) to afford the title compound as a colourless oil (34 mg, 74%).

υ_{max} (neat): 3059, 3019, 2921, 1498 cm^{-1}

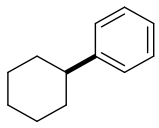
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 4H, 4 x ArH), 7.25 – 7.16 (m, 6H, 6 x ArH), 4.16 (q, 1H, CH, *J* = 7.2 Hz), 1.65 (d, 3H, CH_3, *J* = 7.2 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.5, 128.5, 127.8, 126.2, 44.9, 22.0.

HRMS ($C_{14}H_{14}$) [M] requires: 182.1098, observed: 182.1096

Consistent with reported data.[233]

Compound 109, cyclohexylbenzene



Synthesised according to General Procedure L using bromobenzene (26 µL, 0.25 mmol, 1 equiv.) and 1-cyclohexen-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (100% PE) to afford the title compound a yellow oil (26 mg, 66%).

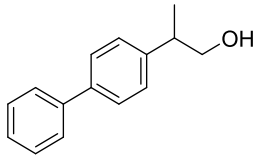
υ_{max} (neat): 2901, 2820, 1440 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H, 2 x ArH), 7.24 – 7.15 (m, 3H, 3 x ArH), 2.55 – 2.46 (m, 1H, CH), 1.92 – 1.82 (m, 4H, 2 x CH_2), 1.79 – 1.73 (m, 1H, CH), 1.47 – 1.37 (m, 4H, 2 x CH_2), 1.30 – 1.26 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 128.4, 127.0, 125.9, 44.8, 34.6, 27.1, 26.3.

HRMS ($C_{12}H_{17}$) $[M+H]^+$ requires: 161.1330, observed: 161.1330

Compound 111, 2-([1,1'-biphenyl]-4-yl)propan-1-ol



Synthesised according to General Procedure L using 2-bromoallyl alcohol (22 µL, 0.25 mmol, 1 equiv.) and 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a clear oil (39 mg, 73%).

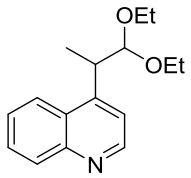
υ_{max} (neat): 3301, 3060, 2902, 1491 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (m, 4H, 4 x ArH), 7.48 – 7.40 (m, 2H, 2 x ArH), 7.37 – 7.29 (m, 3H, 3 x ArH), 3.76 (d, 2H, CH_2, *J* = 6.8 Hz), 3.06 – 2.96 (m, 1H, CH), 1.40 (s, 1H, OH), 1.33 (d, 3H, CH_3 *J* = 7.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.9, 141.1, 139.8, 128.9, 128.1, 127.5, 127.3, 127.2, 68.8, 42.3, 17.7.

HRMS ($C_{15}H_{20}ON$) $[M+NH_4]^+$ requires: 230.1540, observed: 230.1539

Compound 112, 4-(1,1-diethoxypropan-2-yl)quinoline



Synthesised according to General Procedure L using 2-bromo-3,3-diethoxyprop-1-ene (52 mg, 0.25 mmol, 1 equiv.) and 4-quinolineboronic acid (43 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound as a clear oil (46 mg, 71%).

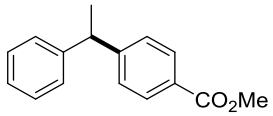
υ_{max} (neat): 2972, 2876, 2359, 2340, 1622, 1582 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H, ArH), 8.53 (s, 1H, ArH), 8.12 (d, 1H, ArH, *J* = 8.6 Hz), 7.96 (d, 1H, ArH, *J* = 8.1 Hz), 7.74 – 7.68 (m, 1H, ArH), 7.61 – 7.55 (m, 1H, ArH), 4.66 (d, 1H, CH, *J* = 6.3 Hz), 3.86 – 3.77 (m, 1H, CH), 3.78 – 3.70 (m, 1H, CH), 3.58 – 3.44 (m, 2H, 2 x CH), 3.32 – 3.28 (m, 1H, CH), 1.47 (d, 3H, *J* = 7.1 Hz, CH_3), 1.20 (t, 3H, CH_3, *J* = 7.0 Hz), 0.90 (t, 3H, CH_3, *J* = 7.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 141.9, 135.1, 130.1, 128.4, 126.7, 123.0, 106.9, 63.6, 37.1, 25.0, 16.5, 15.4,

HRMS ($C_{16}H_{22}O_2N$) $[M+H]^+$ requires: 260.1643, observed: 260.1645

Compound 113, methyl 4-(1-phenylethyl)benzoate



Synthesised according to General Procedure L using α-bromostyrene (36 µL, 0.25 mmol, 1 equiv.) and 4-methoxycarbonylphenylboronic acid (45 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a clear oil (49 mg, 82%).

υ_{max} (neat): 2920, 2852, 1719 cm^{-1}

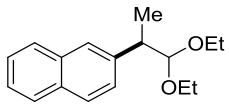
^1H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.93 (m, 2H, 2 x ArH), 7.32 – 7.27 (m, 4H, 4 x ArH), 7.23 – 7.17 (m, 3H, 3 x ArH), 4.20 (q, 1H, CH, *J* = 7.2 Hz), 3.89 (s, 3H, OCH_3), 1.66 (d, 3H, CH_3, *J* = 7.2 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 151.9, 129.9, 128.7, 127.8, 127.8, 126.5, 52.1, 45.0, 21.7 (2C not observed).

HRMS ($C_{16}H_{17}O_2$) $[M+H]^+$ requires: 241.1223, observed: 241.1223

Consistent with reported data.[234]

Compound 114, 2-(1,1-diethoxypropan-2-yl)naphthalene



Synthesised according to General Procedure L using 2-naphthylboronic acid (43 mg, 0.25 mmol, 1 equiv.) and 2-bromo-3,3-diethoxyprop-1-ene (52 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound as a clear oil (34 mg, 53%).

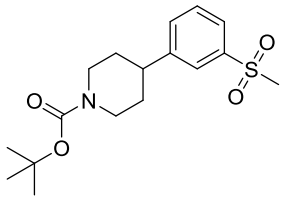
υ_{max} (neat): 2963, 2930, 2851, 1719, 1609 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.76 (m, 3H, 3 x ArH), 7.70 (s, 1H, ArH), 7.49 – 7.40 (m, 3H, 3 x ArH), 4.58 (d, 1H, CH, *J* = 6.5 Hz), 3.74 (dq, 1H, CH, *J* = 9.3, 7.0 Hz), 3.63 – 3.54 (m, 1H, CH), 3.54 – 3.45 (m, 1H, CH), 3.35 (dq, 1H, CH, *J* = 9.3, 7.0 Hz), 3.19 (p, 1H, CH, *J* = 7.0 Hz), 1.40 (d, 3H, CH_3, *J* = 7.1 Hz), 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 1.03 (t, 3 H, CH_3, *J* = 7.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0, 133.6, 132.5, 127.8, 127.7, 127.0, 126.6, 125.9, 125.4, 107.0, 62.9, 44.1, 16.7, 15.4, 15.3.

HRMS ($C_{17}H_{22}O_2NH_4$) $[M+H]^+$ requires: 276.1958, observed: 276.1958.

Compound 118, 4-(3-(methylsulfonyl)phenyl)piperidine



Synthesised according to General Procedure L using 3-bromophenylmethylsulfone (59 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound as a yellow oil (73 mg, 86%).

Synthesised according to General Procedure W using 3-bromophenylmethylsulfone (59 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash

column chromatography (40% EtOAc/PE) to afford the title compound as a yellow oil (76 mg, 89%).

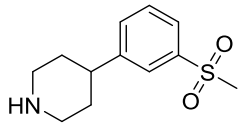
υ_{max} (neat): 2974, 2926, 1683, 1423 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H, 2 x ArH), 7.53 – 7.47 (m, 2H, 2 x ArH), 4.26 (br. s, 2H, CH_2), 3.04 (s, 3H, CH_3), 2.86 – 2.72 (m, 3H, 3 x CH), 1.84 (d, 2H, 2 x CH, *J* = 12.8 Hz), 1.69 – 1.60 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ 154.9, 147.7, 141.0, 132.3, 129.8, 125.7, 125.5, 79.8, 44.6, 42.7, 33.1, 28.6.

HRMS ($C_{17}H_{26}O_4N_2S$) $[M+H]^+$ requires: 357.1843, observed: 357.1843

Compound 119, 4-(3-(methylsulfonyl)phenyl)piperidine



To a vial containing Compound 118 (60 mg, 0.18 mmol, 1 equiv.) was added DCM (1 mL), then TFA (138 μL, 1.8 mmol, 10 equiv.) dropwise. The reaction mixture was stirred at room temperature for 4 hours before being concentrated under compressed air. The crude material was dissolved in minimal MeOH and applied to a 2g SCX cartridge which had been equilibrated with MeOH. The cartridge was washed with 2 column volumes of MeOH, followed by 2 column volumes of NH_3/MeOH (3M). The NH_3/MeOH fractions were combined and concentrated *in vacuo* to afford the title compound as a white amorphous solid (39 mg, 91%).

υ_{max} (neat): 3210, 2901, 1688, 1499, 1300 cm^{-1}

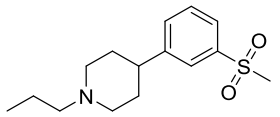
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 – 7.74 (m, 2H, 2 x ArH), 7.53 – 7.47 (m, 2H, 2 x ArH), 3.21 (d, 2H, CH_2, *J* = 12.0 Hz), 3.04 (s, 3H, CH_3), 2.74 (m, 2H, CH_2,), 2.11 (br. s, 1H, NH), 1.86 (d, 2H, CH_2, *J* = 12.8 Hz), 1.67 (q, 2H, CH_2, *J* = 12.4 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 140.8, 132.3, 129.7, 125.8, 125.3, 47.0, 44.6, 43.0, 34.3.

HRMS ($C_{12}H_{18}O_2NS$) $[M+H]^+$ requires: 240.1052, observed: 240.1053

Consistent with reported data.[7]

Compound 117, 4-(3-(methylsulfonyl)phenyl)-1-propylpiperidine



To an oven dried round bottom flask was added K_2CO_3 (45 mg, 0.39 mmol, 2.5 equiv.) and was purged with nitrogen. Compound 119 (30 mg, 0.13 mmol, 1 equiv.) was added in MeCN (2 mL) and the reaction mixture was stirred at room temperature for 15 minutes. 1-Iodopropane (15 μL, 0.16 mmol, 1.2 equiv.) was added dropwise at 0 ˚C and the reaction mixture was heated to 70 ˚C and stirred for 24 h. The reaction was then allowed to cool to room temperature and applied directly to an SCX cartridge which had been equilibrated with MeOH. The cartridge was washed with 2 column volumes of MeOH, followed by 2 column volumes of NH_3/MeOH (3M). The NH_3/MeOH fractions were combined and concentrated *in vacuo* to afford a clear gum which was purified by flash column chromatography (10% MeOH/DCM) to afford the title compound as a colourless gum (25 mg, 69%).

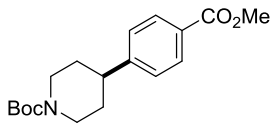
υ_{max} (neat): 2991, 2920, 1646, 1333 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.75 (m, 2H, 2 x ArH), 7.57 – 7.47 (m, 2H, 2 x ArH), 3.19 (d, 2H, 2 x CH, *J* = 11.6 Hz), 3.04 (s, 3H, CH_3), 2.67 (tt, 1H, CH, *J* = 11.9, 4.0 Hz), 2.49 – 2.42 (m, 2H, 2 x CH), 2.20 (t, 2H, 2 x CH, *J* = 11.8 Hz), 2.02 – 1.85 (m, 4H, 4 x CH), 1.68 – 1.58 (m, 2H, 2 x CH), 0.94 (t, 3H, CH_3, *J* = 7.4 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.7, 140.9, 132.2, 129.8, 126.0, 125.4, 60.7, 54.0, 44.6, 42.3, 32.7, 19.8, 12.0.

HRMS ($C_{15}H_{24}O_2NS$) $[M+H]^+$ requires: 282.1528, observed: 282.1532

Compound 125, *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-

dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.). The crude material was taken up in ethyl acetate and washed with water (2 x 10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white amorphous solid (79.6 mg, 99%).

Synthesised according to General Procedure AA using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/PE) to afford the title compound as a white amorphous solid (36.7 mg, 46%).

To the right hand vessel of the COware apparatus was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.), PdXPhosG2 (2 mg, 0.0025 mmol, 0.01 equiv.), 10% Pd/C (32 mg, 0.04 mmol, 0.12 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.) and aryl halide (0.25 mmol, 1 equiv.). The vial was capped and purged, then 1,4-dioxane (800 µL) and water (200 µL) were added. In the left hand vessel was added zinc (650 mg, 10 mmol, 40 eq.). The reaction mixture was stirred at 80 °C for 4 h, followed by the addition of conc. HCl (0.7 mL, 8.25 mmol. 33 eq.) to the left hand vessel. After this, the reaction was stirred for 16 h at room temperature. The vial was de-capped, and the reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed through with further ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography (20% EtOAc/PE) to afford the title compound as a white amorphous solid (76 mg, 95%).

υ_{max} (neat): 2973, 2930, 2848, 1719, 1688 cm^{-1}

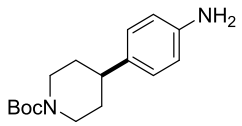
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.26 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 4.25 (br. s, 2H, 2 x CH), 3.89 (s, 3H, CH_3), 2.80 (t, 2H, 2 x CH, *J* = 11.0 Hz), 2.70 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.82 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.62 (qd, 2H, 2 x CH, *J* = 12.7, 4.3 Hz), 1.47 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 154.9, 151.2, 130.0, 128.5, 127.0, 79.7, 52.1, 44.3, 42.9, 33.0, 28.6.

HRMS ($C_{18}H_{26}O_4N$) $[M+H]^+$ requires: 320.1856, observed: 320.1856

Consistent with reported data.[235]

Compound 127, *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 4-bromo nitrobenzene (50 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a white solid (67.6 mg, 98%).

Synthesised according to General Procedure W using benzyl (4-bromophenyl)carbamate (77 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a white solid (53.0 mg, 77%).

Synthesised according to General Procedure AA using 4-bromo nitrobenzene (50 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a white solid (47.6 mg, 69%).

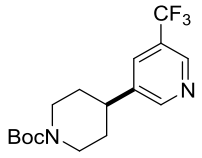
υ_{max} (neat): 3462, 3363, 2985, 2928, 2846, 1667 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 6.64 (d, 2 x ArH, *J* = 8.5 Hz), 4.21 (br. s, 2H, 2 x CH), 3.58 (br. s, 2H, NH_2), 2.77 (t, 2H, 2 x CH, *J* = 12.4 Hz), 2.53 (tt, 1H, CH, *J* = 12.1, 3.6 Hz), 1.77 (d, 2H, 2 x CH, *J* = 13.3 Hz), 1.62 – 1.50 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 144.8, 136.2, 127.7, 115.4, 79.5, 44.6, 42.0, 33.6, 28.6.

HRMS ($C_{16}H_{25}O_2N_2$) $[M+H]^+$ requires: 277.1911, observed: 277.1911

Compound 128, *tert*-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 3-bromo-5-(trifluoromethyl)pyridine (57 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/PE) to afford the title compound as a yellow oil (61.4 mg, 74%).

υ_{max} (neat): 2981, 2858, 1670, 1498 cm^{-1}

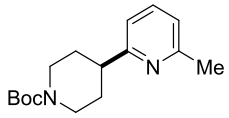
^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H, ArH), 8.67 (s, 1H, ArH), 7.73 (s, 1H, ArH), 4.28 (br. s, 2H, 2 x CH), 2.89 – 2.73 (m, 3H, 3 x CH), 1.86 (d, 2H, 2 x CH, J = 13.3 Hz), 1.75 – 1.58 (m, 3H, 3 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, Acetone): δ 155.2, 153.8, 145.3 ($^3J_{CF}$, q, J = 4.2 Hz) 142.9, 132.2 ($^1J_{CF,}$ q, J = 3.3 Hz), 126.9 ($^2J_{CF,}$ app. d, J = 32.3 Hz), 125.1 ($^1J_{CF,}$ q, J = 272.3 Hz), 79.6, 45.0, 40.8, 33.5, 28.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.42.

HRMS ($C_{16}H_{22}F_3O_2N_2$) $[M+H]^+$ requires: 331.1628, observed: 331.1630

Compound 129, *tert*-butyl 4-(6-methylpyridin-2-yl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 3-bromo-5-(trifluoromethyl)pyridine (28 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound as a yellow oil (40.9 mg, 59%).

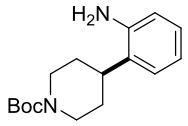
υ_{max} (neat): 2973, 2922, 2852, 1690, cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (t, 1H, ArH, *J* = 7.7 Hz), 6.95 (dd, 2H, 2 x ArH, *J* = 18.4, 7.7 Hz), 4.23 (br. s, 2H, 2 x CH), 2.88 – 2.75 (m, 3H, 3 x CH), 2.52 (s, 3H, CH_3), 1.91 (d, 2H, 2 x CH, *J* = 13.4 Hz), 1.66 (qd, 2H, 2 x CH, *J* = 12.7, 4.8 Hz), 1.47 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.0, 157.9, 155.0, 136.9, 121.2, 117.5, 79.5, 44.9, 44.2, 32.0, 28.6, 24.7.

HRMS ($C_{16}H_{25}O_2N_2$) $[M+H]^+$ requires: 277.1911, observed: 277.1910

Compound 130, *tert*-butyl 4-(2-aminophenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 2-bromo nitrobenzene (51 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (40% EtOAc/PE) to afford the title compound as a dark yellow oil (66.2 mg, 96%).

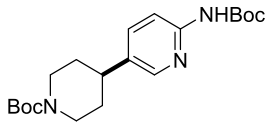
υ_{max} (neat): 3456, 3357, 2971, 2921, 2850, 1677, 1625 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 – 7.02 (m, 2H, 2 x ArH), 6.79 (td, 1H, ArH, *J* = 7.5, 1.1 Hz), 6.70 (dd, 1H, ArH, *J* = 7.9, 1.1 Hz), 4.27 (br. s, 2H, 2 x CH), 3.64 (s, 2H, NH_2), 2.82 (t, 2H, 2 x CH, *J* = 11.3 Hz), 2.62 (tt, 1H, CH, *J* = 11.9, 3.2 Hz), 1.85 (d, 2H, 2 x CH, *J* = 13.3 Hz), 1.61 (qd, 2H, 2 x CH, *J* = 12.7, 4.3 Hz), 1.49 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 154.4, 138.0, 127.9, 115.5, 79.8, 44.7, 41.9, 33.6, 28.7 (2C not observed).

HRMS ($C_{16}H_{25}O_2N_2$) $[M+H]^+$ requires: 277.1911, observed: 277.1911

Compound 131, *tert*-butyl 4-(6-((tert-butoxycarbonyl)amino)pyridin-3-yl)piperidine-1 carboxylate



Synthesised according to General Procedure W using *tert*-butyl (5-bromopyridin-2-yl)carbamate (68 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/PE) to afford the title compound as a white amorphous solid (70.7 mg, 75%).

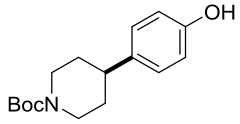
υ_{max} (neat): 3171, 2972, 2858, 1720, 1688 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, NH), 8.14 (d, 1H, ArH, *J* = 2.2 Hz), 7.89 (d, 1H, ArH, *J* = 8.6 Hz), 7.49 (dd, 1H, ArH, *J* = 8.7, 2.4 Hz), 4.23 (br. s, 2H, 2 x CH), 2.78 (t, 2H, 2 x CH, *J* = 12.2 Hz), 2.60 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.78 (d, 2H, 2 x CH, *J* = 12.8 Hz), 1.67 – 1.53 (m, 2H, 2 x CH), 1.53 (s, 9H, 3 x CH_3), 1.47 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9, 152.9, 151.0, 146.2, 136.6, 135.6, 112.5, 80.9, 79.7, 44.3, 39.8, 33.2, 28.6, 28.5.

HRMS ($C_{20}H_{32}N_3O_4$) $[M+H]^+$ requires: 378.2387, observed: 378.2385

Compound 132, *tert*-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 1-(benzyloxy)-4-bromobenzene (66 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a clear oil (53.0 mg, 77%).

υ_{max} (neat): 3317, 3006, 2974, 2932, 2852, 1660 cm^{-1}

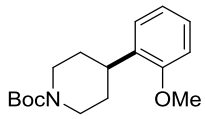
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, 2H, 2 x ArH, *J* = 8.5 Hz), 6.79 (d, 2H, 2 x ArH, *J* = 8.6 Hz), 6.17 (s, 1H, OH), 4.21 (br. s, 2H, 2 x CH), 2.79 (t, 2H, 2 x CH, *J* = 12.0 Hz), 2.56

(tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.77 (d, 2H, 2 x CH, *J* = 14.0 Hz), 1.62 – 1.50 (m, 2H, 2 x CH), 1.49 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 154.7, 137.7, 127.9, 115.5, 79.9, 44.8, 41.9, 33.6, 28.6.

HRMS ($C_{16}H_{24}NO_3$) $[M+H]^+$ requires: 278.1751, observed: 278.1752

Compound 133, *tert*-butyl 4-(2-methoxyphenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 2-bromoanisole (31 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a clear oil (71.3 mg, 98%).

υ_{max} (neat): 2999, 1667, 1520, 1403 cm^{-1}

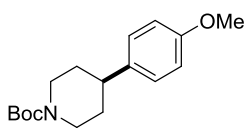
^1H NMR (500 MHz, $CDCl_3$): δ 7.21 – 7.17 (m, 1H, ArH), 7.15 (dd, 1H, ArH, *J* = 7.6, 1.4 Hz), 6.93 (t, 1H, ArH, *J* = 7.5 Hz), 6.86 (d, 1H, ArH, *J* = 8.2 Hz), 4.23 (br. s, 2H, 2 x CH), 3.83 (s, 3H, OCH_3), 3.09 (tt, 1H, CH, *J* = 12.1, 3.4 Hz), 2.83 (t, 2H, 2 x CH, *J* = 11.1 Hz), 1.79 (d, 2H, 2 x CH, *J* = 12.8 Hz,), 1.59 (qd, 2H, 2 x CH, *J* = 12.6, 4.0 Hz), 1.49 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.9, 155.1, 134.0, 127.2, 126.7, 120.8, 110.5, 79.4, 55.4, 44.9, 35.5, 32.0, 28.6.

HRMS ($C_{17}H_{26}O_3N$) $[M+H]^+$ requires: 292.1907, observed: 292.1909

Consistent with reported data.[236]

Compound 134, *tert*-butyl 4-(4-methoxyphenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 4-bromoanisole (31 µL, 0.25 mmol, 1 equiv.) and *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a white solid (51.4 mg, 71%).

υ_{max} (neat): 2980, 1671, 1590, 1501 cm^{-1}

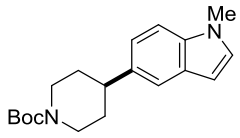
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, 2H, 2 x ArH, *J* = 8.6 Hz), 6.85 (d, 2H, 2 x ArH, *J* = 8.7 Hz), 4.23 (br. s, 2H, 2 x CH), 3.79 (s, 3H, CH_3), 2.79 (t, 2H, 2 x CH, *J* = 11.2 Hz), 2.59 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.79 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.65 – 1.52 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 155.0, 138.2, 127.8, 114.0, 79.5, 55.4, 44.5, 42.0, 33.6, 28.6.

HRMS ($C_{17}H_{26}O_3N$) $[M+H]^+$ requires: 292.1907, observed: 292.1908

Consistent with reported data.[236]

Compound 135, *tert*-butyl 4-(1-methyl-1H-indol-5-yl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 5-bromo-1-methylindole (53 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a clear oil (45.3 mg, 58%).

υ_{max} (neat): 2973, 2928, 2848, 1688, 1422 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H, ArH), 7.27 (d, 1H, ArH, *J* = 8.4 Hz), 7.10 (dd, 1H, ArH, *J* = 8.5, 1.5 Hz), 7.04 (d, 1H, ArH, *J* = 3.1 Hz), 6.44 (d, 1H, ArH, *J* = 3.0 Hz), 4.27 (br. s, 2H, 2 x CH), 3.77 (s, 3H, CH_3), 2.84 (t, 2H, 2 x CH, *J* = 11.1 Hz), 2.75 (tt, 1H, CH, *J*

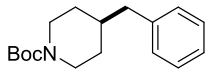
= 12.1, 3.5 Hz), 1.88 (d, 2H, 2 x CH, *J* = 12.9 Hz), 1.71 (qd, 2H, 2 x CH, *J* = 12.7, 4.0 Hz), 1.51 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.1, 137.1, 135.7, 129.2, 128.8, 121.1, 118.5, 109.3, 100.8, 79.5, 44.7, 43.0, 34.1, 33.0, 28.7.

HRMS ($C_{19}H_{26}O_2N_2$) [M] requires: 314.1994, observed: 314.1986

Consistent with reported data.[237]

Compound 136, *tert*-butyl 4-benzylpiperidine-1-carboxylate



Synthesised according to General Procedure W using benzyl bromide (30 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (8% EtOAc/PE) to afford the title compound as a yellow oil (33.0 mg, 48%).

υ_{max} (neat): 3021, 2999, 2939, 1688 cm^{-1}

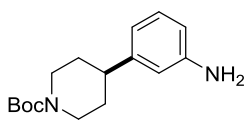
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, 2 x ArH), 7.23 – 7.16 (m, 1H, ArH), 7.16 – 7.11 (m, 2H, 2 x ArH), 4.06 (br. s, 2H, 2 x CH), 2.63 (t, 2H, 2 x CH, *J* = 12.4 Hz), 2.53 (d, 2H, CH_2, *J* = 7.0 Hz), 1.69 – 1.57 (m, 3H, 3 x CH), 1.45 (s, 9H, 3 x CH_3), 1.21 – 1.08 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 140.4, 129.3, 128.4, 126.1, 79.4, 44.1, 43.3, 38.3, 32.1, 28.6.

HRMS ($C_{13}H_{18}ON$) $[M-^tBu+H]^+$ requires: 220.1338, observed: 220.1337

Consistent with reported data.[238]

Compound 137, *tert*-butyl 4-(3-aminophenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 3-bromoaniline (27 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/PE) to afford the title compound as an off-white solid (34.4 mg, 50%).

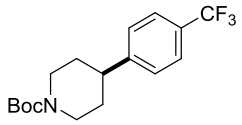
υ_{max} (neat): 3443, 3352, 2935, 2852, 1651, 1604 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.09 (t, 1H, ArH, *J* = 7.9 Hz), 6.60 (d, 1H, ArH, *J* = 7.6 Hz), 6.56 – 6.51 (m, 2H, 2 x ArH), 4.22 (br. s, 2H, 2 x CH), 3.63 (s, 2H, NH_2), 2.77 (t, 2H, 2 x CH, *J* = 10.7 Hz), 2.54 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 1.79 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.65 – 1.53 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 147.3, 146.7, 129.5, 117.3, 113.7, 113.3, 79.5, 44.6, 42.9, 33.2, 28.6.

HRMS ($C_{16}H_{25}O_2N_2$) $[M+H]^+$ requires: 277.1911, observed: 277.1912

Compound 138, *tert*-butyl 4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 4-bromobenzotrifluoride (36 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound as a yellow oil (70.0 mg, 85%).

Synthesised according to General Procedure AA using 4-bromobenzotrifluoride (36 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (6% EtOAc/PE) to afford the title compound as a yellow oil (57.6 mg, 70%).

υ_{max} (neat): 3005, 2931, 2849, 1655 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.31 (d, 2H, 2 x ArH, *J* = 8.1 Hz), 4.26 (br. s, 2H, 2 x CH), 2.81 (t, 2H, 2 x CH, *J* = 11.4 Hz), 2.71 (tt, 1H, CH, *J* = 12.2,

3.5 Hz), 1.82 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.62 (qd, 2H, 2 x CH, *J* = 12.6, 4.1 Hz), 1.48 (s, 9H, 3 x CH_3).

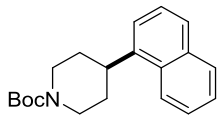
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.0, 149.9, 128.9 ($^2J_{CF}$, q, *J* = 32.3 Hz), 127.3, 125.6 ($^3J_{CF}$, q, *J* = 3.6 Hz), 124.3 ($^1J_{CF}$, q, *J* = 218.2 Hz), 79.7, 44.4, 42.8, 33.1, 28.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.4.

HRMS ($C_{17}H_{23}F_3NO_2$) $[M+H]^+$ requires: 330.1675, observed: 330.1678

Consistent with reported data.[239]

Compound 139, *tert*-butyl 4-(naphthalen-1-yl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 1-bromonapthalene (52 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound as a yellow oil (45.9 mg, 59%).

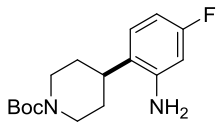
υ_{max} (neat): 2982, 2965, 2924, 2835, 1695 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 3H, 3 x ArH), 7.64 (s, 1H, ArH), 7.49 – 7.41 (m, 2H, 2 x ArH), 7.36 (dd, 1H, ArH, *J* = 8.5, 1.7 Hz), 4.30 (br. s, 2H, 2 x CH), 2.93 – 2.76 (m, 3H, 3 x CH), 1.92 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.74 (qd, 2H, 2 x CH, *J* = 12.7, 4.1 Hz), 1.51 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 143.4, 133.7, 132.4, 128.2, 127.8, 127.7, 126.1, 125.9, 125.5, 124.9, 79.6, 44.6, 42.9, 33.3, 28.6.

HRMS ($C_{20}H_{26}NO_2$) $[M+H]^+$ requires: 312.1958, observed: 312.1958

Compound 140, *tert*-butyl 4-(2-amino-4-fluorophenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 2-bromo-5-fluoroaniline (48 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (35% EtOAc/PE) to afford the title compound as a yellow oil (58.1 mg, 79%).

υ_{max} (neat): 3460, 3363, 2930, 2850, 1673 cm^{-1}

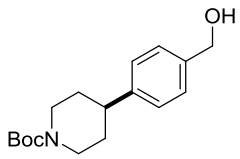
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (dd, 1H, ArH, *J* = 8.6, 6.4 Hz), 6.46 (td, 1H, ArH, *J* = 8.5, 2.6 Hz), 6.39 (dd, 1H, ArH, *J* = 10.5, 2.6 Hz), 4.25 (br. s, 2H, 2 x CH), 2.80 (t, 2H, 2 x CH, *J* = 12.4 Hz), 2.53 (tt, 1H, CH, *J* = 11.9, 3.2 Hz), 1.82 (d, 2H, 2 x CH, *J* = 13.3 Hz), 1.62 – 1.51 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3). 2H not observed (exchangeable).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 ($^{1}J_{CF}$, d, *J* = 242.5 Hz), 155.0, 145.0 ($^{3}J_{CF}$, d, *J* = 10.5 Hz), 127.4 ($^{3}J_{CF}$, d, *J* = 10.1 Hz), 125.4, 105.6 ($^{2}J_{CF}$, d, *J* = 21.1 Hz), 102.8 ($^{2}J_{CF}$, d, *J* = 24.4 Hz), 79.7, 44.7, 36.5, 31.8, 28.6, 25.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.7.

HRMS ($C_{16}H_{24}FO_2N_2$) $[M+H]^+$ requires: 295.1816, observed: 295.1819

Compound 141, *tert*-butyl 4-(4-(hydroxymethyl)phenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 4-bromobenzyl alcohol (47 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a yellow oil (50.1 mg, 69%).

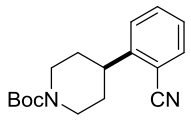
υ_{max} (neat): 3442, 3014, 2910, 2851, 1666 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.19 (d, 2H, 2 x ArH, *J* = 8.1 Hz), 4.66 (s, 2H, CH_2), 4.22 (br. s, 2H, 2 x CH), 2.79 (t, 2H, 2 x CH, *J* = 12.2 Hz), 2.64 (tt, 1H, CH, *J* = 12.1, 3.6 Hz), 1.89 (br. s, 1H, OH), 1.80 (d, 2H, 2 x CH, *J* = 13.5 Hz), 1.60 (qd, 2H, 2 x CH, *J* = 12.7, 4.4 Hz), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 145.4, 139.2, 127.4, 127.1, 79.6, 65.2, 44.5, 42.6, 33.3, 28.6.

HRMS ($C_{17}H_{26}O_3N$) $[M+H]^+$ requires: 292.1907, observed: 292.1909

Compound 142, *tert*-butyl 4-(2-cyanophenyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 2-bromobenzonitrile (46 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a yellow oil (54.0 mg, 76%).

υ_{max} (neat): 2999, 2923, 2222, 1681 cm^{-1}

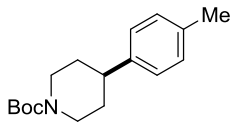
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, 1H, ArH, *J* = 7.7, 1.0 Hz), 7.55 (td, 1H, ArH, *J* = 7.8, 1.2 Hz), 7.31 (ddd, 2H, 2 x ArH, *J* = 9.2, 8.5, 4.4 Hz), 4.27 (br. s, 2H, 2 x CH), 3.13 (tt, 1H, CH, *J* = 12.1, 3.5 Hz), 2.87 (br. s, 2H, 2 x CH), 1.86 (d, 2H, 2 x CH, *J* = 13.1 Hz), 1.71 – 1.57 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.8, 149.2, 133.1, 133.1, 126.9, 126.5, 117.9, 112.0, 79.6, 44.1, 40.9, 32.4, 28.5.

HRMS ($C_{17}H_{23}O_2N_2$) $[M+H]^+$ requires: 287.1754, observed: 287.1755

Consistent with reported data.[240]

Compound 123, *tert*-butyl 4-(p-tolyl)piperidine-1-carboxylate



Synthesised according to General Procedure W using 4-bromotoluene (31µL, 0.25 mmol, 1 equiv.) and *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.). The crude material was taken up in ethyl acetate and washed with water (2 x 10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear oil (68.0 mg, 99%).

Synthesised according to General Procedure AA using 4-bromobenzotrifluoride (36 µL, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (5% EtOAc/PE) to afford the title compound as a yellow oil (67.6 mg, 99%).

υ_{max} (neat): 2971, 2926, 2848, 1688 cm^{-1}

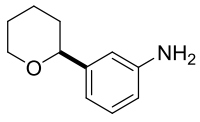
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.09 (m, 4H, 4 x ArH), 4.24 (br. s, 2H), 2.79 (t, 2H, 2 x CH, *J* = 11.4 Hz), 2.60 (tt, 1H, *J* = 12.1, 3.5 Hz), 2.32 (s, 3H, CH_3), 1.80 (d, 2H, 2 x CH, *J* = 13.1 Hz), 1.69 – 1.55 (m, 2H, 2 x CH), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 143.0, 136.0, 129.3, 126.8, 79.5, 44.6, 42.4, 33.4, 28.6, 21.1.

HRMS ($C_{17}H_{26}O_2N$) $[M+H]^+$ requires: 276.1958, observed: 276.1958

Consistent with reported data.[239]

Compound 143, 3-(tetrahydro-2*H*-pyran-2-yl)aniline



Synthesised according to General Procedure W using 2-(3,4-dihydro-2*H*-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53 mg, 0.25 mmol, 1 equiv.) and 3-nitrobromobenzene (50 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (30% EtOAc/PE) to afford the title compound as a clear oil (24.0 mg, 55%).

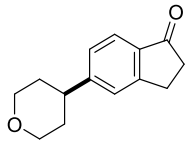
υ_{max} (neat): 3390, 3313, 3067, 2993, 2961, 2806, 1645, 1501 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (t, 1H, ArH, *J* = 7.9 Hz), 6.74 – 6.69 (m, 2H, 2 x ArH), 6.58 (dd, 1H, ArH, *J* = 7.9, 1.4 Hz), 4.24 (dd, 1H, CH, *J* = 10.7, 1.9 Hz), 4.17 – 4.09 (m, 1H, CH), 3.60 (td, 1H, CH, *J* = 11.7, 2.4 Hz), 1.96 – 1.90 (m, 1H, CH), 1.84 – 1.78 (m, 1H, CH), 1.71 – 1.55 (m, 4H, 4 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.5, 144.8, 129.3, 116.4, 114.3, 112.7, 80.3, 69.1, 34.1, 26.1, 24.2.

HRMS ($C_{11}H_{16}ON$) $[M+H]^+$ requires: 178.1226, observed: 178.1223

Compound 93, 5-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-amine



Synthesised according to General Procedure W using 5-bromo-1-indanone (53 mg, 0.25 mmol, 1 equiv.) and 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (53 mg, 0.25 mmol, 1 eq.) and purified by flash column chromatography (25% EtOAc/PE) to afford the title compound an off-white amorphous solid (43.2mg, 80%).

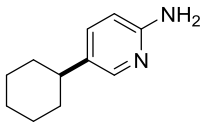
υ_{max} (neat): 2949, 2930, 2846, 1701, 1610 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 1H, ArH, *J* = 8.2 Hz), 7.34 – 7.31 (m, 1H, ArH), 7.24 (ddd, 1H, ArH, *J* = 7.9, 1.4, 0.6 Hz), 4.12 – 4.07 (m, 2H, 2 x CH), 3.54 (td, 2H, 2 x CH, *J* = 11.7, 2.4 Hz), 3.14 – 3.10 (m, 2H, CH_2), 2.85 (tt, 1H, CH, *J* = 11.8, 4.1 Hz), 2.70 – 2.66 (m, 2H, 2 x CH), 1.89 – 1.75 (m, 4H, 2 x CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.6, 156.0, 153.4, 135.8, 126.7, 124.8, 124.0, 68.3, 42.3, 36.6, 33.8, 25.9.

HRMS ($C_{14}H_{17}O_2$) $[M+H]^+$ requires: 217.1229, observed: 217.1233

Compound 144, 5-cyclohexylpyridin-2-amine



Synthesised according to General Procedure W using 5-bromo-2-nitropyridine (51 mg, 0.25 mmol, 1 equiv.) and 1-cyclohexen-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (80% PE/EtOAc) to afford the title compound an off-white amorphous solid (40 mg, 90%).

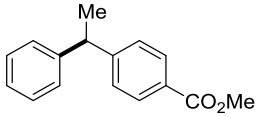
υ_{max} (neat): 3441, 3304, 3144, 2918, 2847, 1639, 1505 cm^{-1}

^{1}H NMR (600 MHz, acetone-d_6) δ 7.82 (d, 1H, ArH, *J* = 1.8 Hz), 7.27 (dd, 1H, ArH, *J* = 8.4, 2.3 Hz), 6.47 (d, 1H, ArH, *J* = 8.4 Hz), 5.11 (br. s, 2H, NH_2), 2.40 – 2.33 (m, 1H, CH), 1.84 – 1.74 (m, 4H, 4 x CH), 1.74 – 1.68 (m, 1H, CH), 1.41 – 1.35 (m, 4H, 4 x CH), 1.28 – 1.22 (m, 1H, CH).

^{13}C NMR (151 MHz, acetone-d_6): δ 159.1, 147.0, 136.4, 132.5, 108.7, 42.0, 35.3, 27.6, 26.7.

HRMS ($C_{11}H_{17}N_2$) [$M+H^{+}$]requires: 177.1383, observed: 177.1386

Compound 113, methyl 4-(1-phenylethyl)benzoate



Synthesised according to General Procedure W using α-bromostyrene (36 µL, 0.25 mmol, 1 equiv.) and 4-methoxycarbonylphenylboronic acid (45 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound as a clear oil (49 mg, 82%).

υ_{max} (neat): 2920, 2852, 1719 cm^{-1}

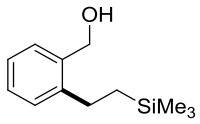
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.93 (m, 2H, 2 x ArH), 7.32 – 7.27 (m, 4H, 4 x ArH), 7.23 – 7.17 (m, 3H, 3 x ArH), 4.20 (q, 1H, CH, *J* = 7.2 Hz), 3.89 (s, 3H, CH_3), 1.66 (d, 3H, CH_3, *J* = 7.2 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 151.9, 129.9, 128.7, 127.8, 127.8, 126.5, 52.1, 45.0, 21.7 (2C not observed).

HRMS ($C_{16}H_{17}O_2$) $[M+H]^+$ requires: 241.1223, observed: 241.1223

Consistent with reported data.[234]

Compound 145, (2-(2-(trimethylsilyl)ethyl)phenyl)methanol



Synthesised according to General Procedure W using (2-(hydroxymethyl)phenyl)boronic acid (38 mg, 0.25 mmol, 1 equiv.) and (*E*)-(2-bromovinyl)trimethylsilane (45 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% PE/EtOAc) to afford the title compound a clear oil (33.6 mg, 65%).

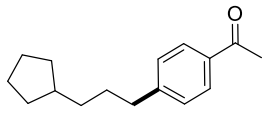
υ_{max} (neat): 3290 (br.), 2948, 2891, 1247 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H. ArH, *J* = 7.3 Hz), 7.29 – 7.19 (m, 3H, 3 x ArH), 4.74 (s, 2H, CH_2), 2.73 – 2.65 (m, 2H, CH_2), 0.89 – 0.82 (m, 2H, CH_2), 0.08 (s, 9H, 3 x CH_3) (1H not observed, exchangeable).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 137.9, 128.8, 128.2, 126.1, 63.1, 26.5, 18.9, -1.7 (1C not observed).

HRMS ($C_{12}H_{21}OSi$) $[M-H]^-$ requires: 207.1205, observed: 207.1207

Compound 146, 1-(4-(3-cyclopentylpropyl)phenyl)ethan-1-one



Synthesised according to General Procedure W, using (E)-2-(3-cyclopentylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59 mg, 0.25 mmol, 1 equiv.) and 4 bromoacetophenone (50 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (8% EtOAc/PE) to afford the title compound as a clear oil (28.5 mg, 60%).

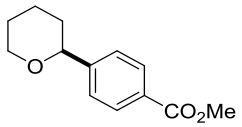
υ_{max} (neat): 2934, 2855, 1680, 1606, 1266 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.24 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 2.67 – 2.60 (m, 2H, 2 x CH), 2.55 (s, 3H, CH_3), 1.73 – 1.68 (m, 2H, 2 x CH), 1.65 – 1.59 (m, 2H, 2 x CH), 1.58 – 1.52 (m, 2H, 2 x CH), 1.50 – 1.42 (m, 2H, 2 x CH), 1.34 – 1.28 (m, 2H, 2 x CH), 1.24 – 1.20 (m, 1H, CH), 1.07 – 1.00 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 149.0, 135.1, 128.7, 128.6, 127.4, 40.1, 36.4, 35.9, 32.8, 30.4, 26.7, 25.3.

HRMS ($C_{16}H_{22}O$) [M] requires: 230.1671, observed: 230.1670

Compound 147, methyl 4-(tetrahydro-2*H*-pyran-2-yl)benzoate



Synthesised according to General Procedure W using 2-(3,4-dihydro-2H-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53 mg, 0.25 mmol, 1 equiv.) and methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (12% EtOAc/PE) to afford the title compound as a clear oil (32.5 mg, 59%).

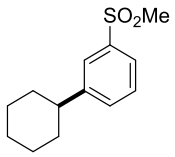
υ_{max} (neat): 2937, 2844, 1714, 1610, 1437 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.41 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 4.38 (dd, 1H, CH, *J* = 11.1, 2.0 Hz), 4.18 – 4.13 (m, 1H, CH), 3.90 (s, 3H, CH_3), 3.62 (td, 1H, CH, *J* = 11.6, 2.5 Hz), 1.98 – 1.91 (m, 1H, CH), 1.85 (d, 1H, CH, *J* = 13.2 Hz), 1.73 – 1.65 (m, 2H, 2 x CH), 1.62 – 1.51 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 148.7, 129.8, 129.1, 125.8, 79.7, 69.1, 52.2, 34.3, 25.9, 24.0.

HRMS ($C_{13}H_{17}O_3$) $[M+H]^+$ requires: 221.1178, observed: 221.1183

Compound 148, 1-cyclohexyl-3-(methylsulfonyl)benzene



Synthesised according to General Procedure W using 4-bromophenyl methyl sulfone (59 mg, 0.25 mmol, 1 equiv.) and 1-cyclohexen-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (30% PE/EtOAc) to afford the title compound an off-white solid (48.2 mg, 81%).

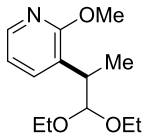
υ_{max} (neat): 2921, 2848, 1597, 1297, 1143 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H, ArH), 7.74 (dt, 1H, ArH, *J* = 6.4, 2.1 Hz), 7.50 – 7.44 (m, 2H, 2 x ArH), 3.04 (s, 3H, CH_3), 2.60 (ddd, 1H, CH, *J* = 11.8, 7.4, 3.2 Hz), 1.92 – 1.82 (m, 4H, 4 x CH), 1.80 – 1.72 (m, 1H, CH), 1.49 – 1.36 (m, 4H, 4 x CH), 1.31 – 1.23 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 140.6, 132.5, 129.4, 125.7, 124.9, 44.7, 44.6, 34.3, 26.8, 26.0.

HRMS ($C_{13}H_{19}O_2S$) $[M+H]^+$ requires: 239.1106, observed: 239.1107

Compound 149, 3-(1,1-diethoxypropan-2-yl)-2-methoxypyridine



Synthesised according to General Procedure W using 2-bromopropenal diethyl acetal (42 µL, 0.25 mmol, 1 equiv.) and 2-methoxy-3-pyridinylboronic acid (38 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/PE) to afford the title compound a colourless oil (32.4 mg, 54%).

υ_{max} (neat): 2973, 2876, 1584, 1461, 1413 cm^{-1}

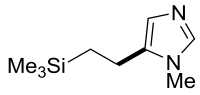
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (dd, 1H, ArH, *J* = 5.0, 1.8 Hz), 7.51 (dd, 1H, ArH, *J* = 7.3, 1.8 Hz), 6.83 (dd, 1H, ArH, *J* = 7.3, 5.0 Hz), 4.60 (d, 1H, CH, *J* = 5.8 Hz), 3.95 (s, 3H, CH_3), 3.69 (dq, 1H, CH, *J* = 9.3, 7.0 Hz), 3.58 (dq, 1H, CH, *J* = 9.4, 7.0 Hz), 3.48 – 3.38 (m,

2H, 2 x CH), 3.38 – 3.31 (m, 1H, CH), 1.25 (d, 3H, CH_3, J = 7.1 Hz), 1.14 (t, 3H, CH_3, J = 7.0 Hz), 1.08 (t, 3H, CH_3, J = 7.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 144.4, 137.3, 125.9, 116.9, 105.2, 63.3, 62.4, 53.4, 37.1, 15.3, 14.6.

HRMS ($C_{13}H_{22}O_3N$) $[M+H]^+$ requires: 240.1594, observed: 240.1592

Compound 150, 1-methyl-5-(2-(trimethylsilyl)ethyl)-1*H*-imidazole



Synthesised according to General Procedure W using (2-bromovinyl)trimethylsilane (45 mg, 0.25 mmol, 1 equiv.) 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-imidazole (52 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (7% PE/EtOAc) to afford the title compound an off-white solid (32.1mg, 71%).

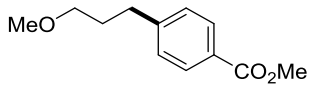
υ_{max} (neat): 2921, 2850, 1736 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, 1H, ArH, J = 1.8 Hz), 6.02 (d, 1H, ArH, J = 1.7 Hz), 3.77 (s, 3H, CH_3), 2.60 – 2.54 (m, 2H, CH_2), 0.90 – 0.84 (m, 2H, CH_2), 0.04 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.4, 138.1, 103.8, 36.1, 20.2, 15.6, -1.7.

HRMS ($C_9H_{19}N_2Si$) $[M+H]^+$ requires: 183.1318, observed: 183.1321

Compound 151, methyl 4-(3-methoxypropyl)benzoate



Synthesised according to General Procedure W using using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and *trans*-3-methoxy-1-propenylboronic acid pinacol ester (50 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (15% EtOAc/PE) to afford the title compound an yellow oil (30.6 mg, 59%).

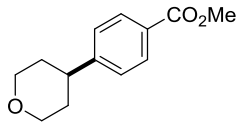
υ_{max} (neat): 2973, 2922, 1690, 1167 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.25 (d, 2H, 2 x ArH, *J* = 8.4 Hz), 3.90 (s, 3H, CH_3), 3.37 (t, 2H, 2 x CH, *J* = 6.3 Hz), 3.34 (s, 3H, CH_3, *J* = 2.6 Hz), 2.78 – 2.70 (m, 2H, 2 x CH), 1.94 – 1.86 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 147.7, 129.9, 128.6, 128.0, 71.8, 58.7, 52.1, 32.5, 31.0.

HRMS ($C_{12}H_{17}O_3$) $[M+H]^+$ requires: 209.1178, observed: 209.1181

Compound 152, methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate



Synthesised according to General Procedure W using methyl 4-bromobenzoate (54 mg, 0.25 mmol, 1 equiv.) and MeOH (1 mL) and purified by flash column chromatography (25% EtOAc/PE) to afford the title compound as an off white amorphous solid (47.3 mg, 86%).

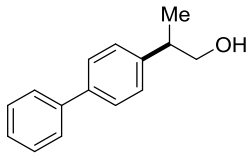
υ_{max} (neat): 3099, 2983, 2799, 1744 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.29 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 4.09 (dd, 2H, 2 x CH, *J* = 11.2, 3.9 Hz), 3.90 (s, 3H, CH_3), 3.53 (td, 2H, 2 x CH, *J* = 11.6, 2.3 Hz), 2.82 (tt, 1H, CH, *J* = 11.7, 4.1 Hz), 1.87 – 1.85 (m, 4H, 2 x CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.1, 151.2, 130.0, 128.4, 126.9, 68.3, 52.1, 41.8, 33.7.

HRMS ($C_{13}H_{16}O_3Na$) $[M+Na]^+$ requires: 243.0993, observed: 243.0992

Compound 153, 2-([1,1'-biphenyl]-4-yl)propan-1-ol



Synthesised according to General Procedure W using 2-bromoallyl alcohol (22 µL, 0.25 mmol, 1 equiv.) and 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (70% EtOAc/PE) to afford the title compound a clear oil (39 mg, 73%).

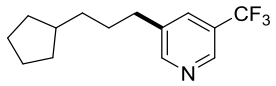
υ_{max} (neat): 3301, 3060, 2902, 1491 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (m, 4H, 4 x ArH), 7.48 – 7.40 (m, 2H, 2 x ArH), 7.37 – 7.29 (m, 3H, 3 x ArH), 3.76 (d, 2H, CH_2, *J* = 6.8 Hz), 3.06 – 2.96 (m, 1H, CH), 1.40 (s, 1H, OH), 1.33 (d, 3H, CH_3 *J* = 7.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.9, 141.1, 139.8, 128.9, 128.1, 127.5, 127.3, 127.2, 68.8, 42.3, 17.7.

HRMS ($C_{15}H_{20}ON$) $[M+NH_4]^+$ requires: 230.1540, observed: 230.1539

Compound 154, 3-(3-cyclopentylpropyl)-5-(trifluoromethyl)pyridine



Synthesised according to General Procedure W using using 3-bromo-5-(trifluoromethyl)pyridine (57 mg, 0.25 mmol, 1 equiv.) and (*E*)-2-(3-cyclopentylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (8% EtOAc/PE) to afford the title compound an yellow oil (33.6 mg, 52%).

υ_{max} (neat): 2941, 2861, 1338, 1132 cm^{-1}

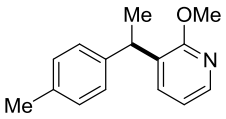
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H, ArH), 8.63 (s, 1H, ArH), 7.71 (s, 1H, ArH), 2.71 – 2.65 (m, 2H, 2 x CH), 1.78 – 1.74 (m, 2H, 2 x CH), 1.72 – 1.62 (m, 3H, 3 x CH), 1.62 – 1.54 (m, 2H, 2 x CH), 1.54 – 1.45 (m, 2H, 2 x CH), 1.40 – 1.31 (m, 2H, 2 x CH), 1.13 – 0.99 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 144.1 ($^{3}J_{CF}$, q, *J* = 4.0 Hz), 138.4, 132.7 ($^{3}J_{CF}$, q, *J* = 3.7 Hz), 123.8 ($^{1}J_{CF}$, q, *J* = 247.3 Hz), 40.0, 35.8, 33.2, 32.8, 30.2, 25.3 (1C not observed).

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.43.

HRMS ($C_{14}H_{19}F_3N$) $[M+H]^+$ requires: 258.1470, observed: 258.1466

Compound 155, 2-methoxy-3-(1-(*p*-tolyl)ethyl)pyridine



Synthesised according to General Procedure W using 1-(1-bromovinyl)-4-methylbenzene (49 mg, 0.25 mmol, 1 equiv.) and (2-methoxypyridin-3-yl)boronic acid (38 mg, 0.25 mmol, 1 equiv.) and purified by flash column chromatography (6% EtOAc/PE) to afford the title compound as a clear oil (34.0 mg, 60%).

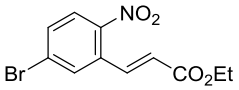
υ_{max} (neat): 3421, 2928, 1703, 1409, 1323 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, 1H, ArH, *J* = 5.0, 1.9 Hz), 7.37 (ddd, 1H, ArH, *J* = 7.3, 1.8, 0.5 Hz), 7.11 (app. q, 4H, 4 x ArH, *J* = 8.3 Hz), 6.81 (dd, 1H, ArH, *J* = 7.3, 5.0 Hz), 4.40 (q, 1H, CH, *J* = 7.2 Hz), 3.93 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.55 (d, 3H, CH_3, *J* = 7.2 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.6, 144.3, 142.2, 135.8, 135.7, 129.5, 129.1, 127.7, 116.9, 53.5, 37.4, 21.1, 20.6.

HRMS ($C_{15}H_{18}ON$) $[M+H]^+$ requires: 228.1383, observed: 228.1382

Compound 156, Ethyl 3-(5-bromo-2-nitrophenyl)acrylate (*20:1, E:Z*)



To a round bottom flask containing 5-bromo-2-nitrobenzaldehyde (300 mg, 1.3 mmol, 1 eq.) and triphenylcarbethoxymethylenephosphorane (1.044 g, 3 mmol, 2.3 eq.) was added DCM (6 mL). The reaction was stirred at room temperature for 16 h before being washed with water (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 before being concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/PE) afforded the title compound a yellow amorphous solid (385 mg, 99%).

υ_{max} (neat): 3096, 2977, 1727, 1709 cm^{-1}

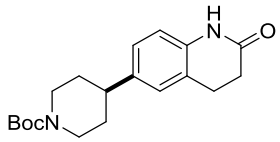
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, 1H, alkene CH, *J* = 15.8 Hz), 7.95 (d, 1H, ArH, *J* = 8.7 Hz), 7.78 (d, 1H, ArH, *J* = 2.1 Hz), 7.67 (dd, 1H, ArH, *J* = 8.7, 2.1 Hz), 6.37 (d, 1H, alkene CH, *J* = 15.8 Hz), 4.30 (q, 2H, CH_2, *J* = 7.1 Hz), 1.35 (t, 3H, CH_3, *J* = 7.1 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 147.0, 138.8, 133.3, 132.7, 132.2, 128.5, 126.5, 124.6, 61.2, 14.3.

(Inconsequential *Z* (~5%) isomer observed in ^{1}H and ^{13}C NMR but not reported).

HRMS ($C_{11}H_{11}NO_4Br$) $[M+H]^+$ requires: 299.9872, observed: 299.9868

Compound 157, *tert*-butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)piperidine-1-carboxylate



Synthesised according to General Procedure W using ethyl (*E)*-3-(5-bromo-2-nitrophenyl)acrylate (75 mg, 0.25 mmol, 1 equiv.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-6-dihydropyridine-1(2*H*)-carboxylate (77 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (60% EtOAc/PE) to afford the title compound as a white solid (65.9 mg, 80%).

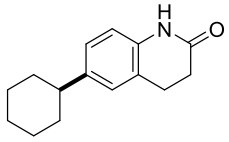
υ_{max} (neat): 3066, 2944, 1683, 1670 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H, NH), 7.03 – 6.96 (m, 2H, 2 x ArH), 6.73 (d, 1H, ArH, *J* = 8.7 Hz), 4.22 (br. s, 2H, 2 x CH), 2.97 – 2.91 (m, 2H, 2 x CH), 2.78 (t, 2H, 2 x CH, *J* = 12.3 Hz), 2.66 – 2.53 (m, 3H, 3 x CH), 1.79 (d, 2H, 2 x CH, *J* = 13.0 Hz), 1.58 (ddd, 2H, 2 x CH, *J* = 25.4, 12.8, 4.3 Hz), 1.48 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 155.0, 141.0, 135.7, 126.5, 125.9, 123.9, 115.6, 79.6, 44.5, 42.3, 33.5, 30.9, 28.6, 25.6.

HRMS ($C_{19}H_{27}O_3N_2$) $[M+H]^+$ requires: 331.2016, observed: 331.2018

Compound 158, 6-cyclohexyl-3,4-dihydroquinolin-2(1H)-one



Synthesised according to General Procedure W using 1-cyclohexen-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.) and ethyl (E)-3-(5-bromo-2-nitrophenyl)acrylate (75 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography (50% EtOAc/PE) to afford the title compound an off-white amorphous solid (40.5 mg, 71%).

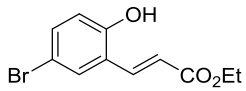
υ_{max} (neat): 3052, 2921, 2834, 1694 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (s, 1H, NH), 7.01 (d, 2H, 2 x ArH, *J* = 6.9 Hz), 6.73 (d, 1H, ArH, *J* = 8.6 Hz), 2.94 (t, 2H, 2 x CH, *J* = 7.6 Hz), 2.65 – 2.60 (t, 2H, 2 x CH, *J* = 7.6 Hz), 2.48 – 2.40 (m, 1H, CH), 1.89 – 1.79 (m, 4H, 4 x CH), 1.74 (d, 1H, CH, *J* = 13.1 Hz), 1.44 – 1.32 (m, 4H, 4 x CH), 1.30 – 1.18 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 143.3, 135.2, 126.5, 125.9, 123.6, 115.4, 44.1, 34.7, 31.0, 27.0, 26.3, 25.7.

HRMS ($C_{15}H_{20}NO$) $[M+H]^+$ requires: 230.1539, observed: 230.1538

Compound 159, ethyl (*E*)-3-(5-bromo-2-hydroxyphenyl)acrylate



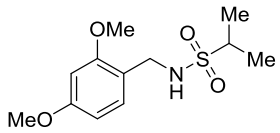
To a round bottom flask containing 5-bromo-2-hydroxybenzaldehyde (200 mg, 1 mmol, 1 eq.) and triphenylcarbethoxymethylenephosphorane (835 mg, 2.3 mmol, 2.3 eq.) was added DCM (5 mL). The reaction was stirred at room temperature for 16 h before being washed with water (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 before being concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/PE) afforded the title compound as a yellow amorphous solid (385 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H, alkene CH, *J* = 16.2 Hz), 7.57 (d, 1H, ArH, *J* = 2.4 Hz), 7.36 – 7.28 (m, 2H, 2 x ArH), 6.77 (d, 1H, ArH, *J* = 8.6 Hz), 6.63 (d, 1H, alkene CH, *J* = 16.2 Hz), 4.30 (q, 2H, CH_2, *J* = 7.1 Hz), 1.36 (t, 3H, CH_3, *J* = 7.1 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 154.8, 139.6, 134.0, 131.5, 123.8, 119.4, 118.3, 112.7, 61.2, 14.4.

Consistent with reported data.[241]

Compound 168, *N*-(2,4-dimethoxybenzyl)propane-2-sulfonamide



N-(2,4-dimethoxybenzyl)propane-2-sulfonamide To an oven dried round bottom flask containing 2,4-dimethoxybenzylamine (417 mg, 2.5 mmol, 1 eq.) in DCM (10 mL) was added Et_3N (1043 µL, 7.5 mmol, 3 eq.) at room temperature. The reaction mixture was cooled to 0 ^oC and 2-propanesulfonyl chloride (280 µL, 2.5 mmol, 1 eq.) was added dropwise. The reaction was stirred at room temperature for 3 hours before being quenched with water then washed between 1 M HCl and DCM, and then water and DCM. The organic layers were dried with Na_2SO_4 and concentrated *in vacuo* before being purified by flash chromatography (40% EtOAc) to afford the title compound as a yellow solid (552.8 mg, 81%).

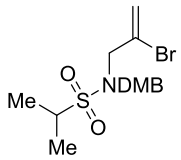
υ_{max} (neat): 3275, 2936, 2836, 1612 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 1H, ArH, J = 8.1 Hz), 6.48 – 6.41 (m, 2H, 2 x ArH), 4.69 (t, 1H, CH, J = 5.9 Hz), 4.22 (d, 2H, CH_2, J = 6.2 Hz), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.95 (hept, 1H, CH, J = 6.8 Hz), 1.27 (d, 6H, 2 x CH_3, J = 6.8 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.1, 158.7, 130.6, 118.2, 104.2, 98.8, 55.6, 55.5, 53.6, 43.8, 16.6.

HRMS ($C_{12}H_{19}NO_4SNa$) $[M+Na]^+$ requires: 296.0927, observed: 296.0928

Compound 169, N-(2-bromoallyl)-*N*-(2,4-dimethoxybenzyl)propane-2-sulfonamide



To a round bottom flask containing *N*-(2,4-dimethoxybenzyl)propane-2-sulfonamide (532 mg, 1.95 mmol, 1 eq.) in MeCN (10 mL) was added Cs_2CO_3 (950 mg, 2.93, 1.5 eq.) at 0 ^oC. After stirring for 5 minutes, 2,3-dibromopropene (80%) (286 µL, 2.34 mmol, 1.2 eq.) was added at 0 ^oC. The reaction mixture was then stirred at 80 ^oC for 2 hours before being quenched with water and washed between water and EtOAc. The organic layers were then dried with Na_2SO_4

and concentrated in vacuo before being purified by flash chromatography (30% EtOAc) to afford the title compound as a yellow oil (588.4 mg, 77%).

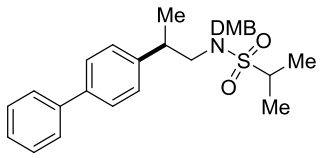
υ_{max} (neat): 2973, 2936, 1612, 1588 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, 1H, ArH, *J* = 8.2 Hz), 6.46 – 6.41 (m, 2H, 2 x ArH), 5.84 (d, 1H, CH, *J* = 1.3 Hz), 5.60 (br. s, 1H, CH), 4.39 (s, 2H, 2 x CH), 4.02 (s, 2H, 2 x CH), 3.78 (s, 6H, 2 x CH_3), 3.05 (hept, 1H, CH, *J* = 6.8 Hz), 1.26 (d, 6H, 2 x CH_3, *J* = 6.9 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.0, 158.7, 131.9, 128.8, 118.6, 116.1, 104.3, 98.4, 55.4, 55.2, 54.6, 46.0, 16.5.

HRMS ($C_{15}H_{22}BrNO_4SNa$) $[M+Na]^+$ requires: 414.0345, observed: 414.0344

Compound 170, *N*-(2-([1,1'-biphenyl]-4-yl)propyl)-N-(2,4-dimethoxybenzyl)propane-2-sulfonamide



Synthesised according to General Procedure X using *N*-(2-bromoallyl)-*N*-(2,4-dimethoxybenzyl)propane-2-sulfonamide (98 mg, 0.25 mmol, 1 equiv.) and 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv.), and purified by flash column chromatography to afford the title compound as a white solid (116.7 mg, 71%).

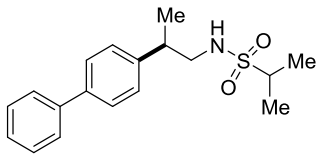
υ_{max} (neat): 2931, 2834, 1612, 1508 cm^{-1}

^{1}H NMR (400 MHz, Acetone): δ 7.66 – 7.56 (m, 4H, 4 x ArH), 7.47 – 7.41 (m, 2H, 2 x ArH), 7.38 – 7.28 (m, 4H, 4 x ArH), 6.59 (d, 1H, ArH, *J* = 2.4 Hz), 6.55 (dd, 1H, ArH, *J* = 8.3, 2.4 Hz), 4.45 (d, 1H, CH, *J* = 15.0 Hz), 4.29 (d, 1H, CH, *J* = 15.0 Hz), 3.89 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.38 (qd, 2H, 2 x CH, *J* = 14.2, 7.6 Hz), 3.17 – 3.05 (m, 1H, CH), 2.91 (dt, 1H, CH, *J* = 13.6, 6.8 Hz), 1.22 (d, 3H, CH_3, *J* = 7.0 Hz), 1.14 (dd, 6H, 2 x CH_3, *J* = 6.8, 1.7 Hz).

^{13}C NMR (101 MHz, Acetone): δ 161.9, 159.7, 144.9, 141.7, 140.2, 132.6, 129.7, 128.8, 128.0, 127.8, 127.6, 117.7, 105.6, 99.0, 55.8, 55.7, 54.1, 46.3, 39.1, 19.4, 17.0, 16.9.

HRMS ($C_{27}H_{34}NO_4S$) $[M+H]^+$ requires: 468.2203, observed: 468.2201

Compound 171, N-(2-([1,1'-biphenyl]-4-yl)propyl)propane-2-sulfonamide



To a solution of *N*-(2-([1,1'-biphenyl]-4-yl)propyl)-*N*-(2,4-dimethoxybenzyl)propane-2-sulfonamide (100 mg, 0.21 mmol, 1 eq.) in DCM (2 mL) was added TFA (161 µL, 2.1 mmol, 10 eq.). The reaction was stirred for 1 h at room temperature before being concentrated *in vacuo*. The crude material was dissolved in minimal MeOH and applied to a 2g SCX cartridge which had been equilibrated with MeOH. The cartridge was washed with 2 column volumes of MeOH, followed by 2 column volumes of NH_3/MeOH (3M). The NH_3/MeOH fractions were combined and concentrated *in vacuo* to afford the title compound as an off-white amorphous solid (64.5 mg, 97%).

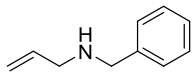
υ_{max} (neat): 3284, 2925, 1612, 1315 cm^{-1}

^{1}H NMR (400 MHz, Acetone): δ 7.70 – 7.57 (m, 4H, 4 x ArH), 7.48 – 7.42 (m, 2H, 2 x ArH), 7.39 – 7.32 (m, 3H, 3 x ArH), 5.88 (app. t, 1H, NH, *J* = 5.8 Hz), 3.39 – 3.25 (m, 2H, 2 x CH), 3.14 – 3.00 (m, 2H, 2 x CH), 1.34 (d, 3H, CH_3, *J* = 7.0 Hz), 1.25 (d, 1H, *J* = 6.8 Hz), 1.21 (d, 1H, *J* = 6.8 Hz).

^{13}C NMR (101 MHz, Acetone): δ 144.6, 141.7, 140.1, 129.7, 128.8, 128.0, 127.8, 127.6, 53.0, 50.9, 41.4, 19.5, 16.9, 16.8.

HRMS ($C_{18}H_{24}NO_2S$) $[M+H]^+$ requires: 318.1522, observed: 318.1527

Compound 176, *N*-benzylprop-2-en-1-amine



To a solution of allyl amine (757 µL, 10 mmol, 1 eq.) in DCM (20 mL) was added Et_3N (2086 µL, 15 mmol, 1.5 eq.) and benzyl bromide (1200 µL, 10 mmol, 1 eq.) at room temperature. The reaction was stirred at room temperature for 1 hour then diluted with water and washed between brine and DCM. The organic layers were dried with Na_2SO_4, concentrated in vacuo

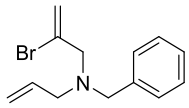
then purified by flash chromatography (20% EtOAc/PE) to afford the title compound as a yellow oil (1378 mg, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (app. d, 4H, 4 x ArH, *J* = 4.4 Hz), 7.28 – 7.23 (m, 1H, ArH), 5.94 (ddt, 1H, CH, *J* = 16.3, 10.3, 6.0 Hz), 5.20 (dq, 1H, CH, *J* = 17.2, 1.6 Hz), 5.12 (app.dd, 1H, CH, *J* = 10.3, 1.5 Hz), 3.80 (s, 2H, CH_2), 3.29 (dt, CH_2, *J* = 6.0, 1.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5, 137.0, 128.5, 128.3, 127.1, 116.1, 53.4, 51.9.

Consistent with reported data.[242]

Compound 177, *N*-allyl-*N*-benzyl-2-bromoprop-2-en-1-amine



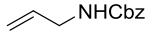
To a solution of *N*-benzylprop-2-en-1-amine (735 mg, 5 mmol, 1 eq.) in MeCN (10 mL) was added Et_3N (1043 µL, 7.5 mmol, 1.5 eq.) and 2,3-dibromopropene (80% purity, 611 µL, 5 mmol, 1 eq.). The reaction was stirred at room temperature for 16 hours before being concentrated *in vacuo* an purified directly by flash chromatography (10% EtOAc/PE) to afford the title compound as a clear oil (850 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, 2H, 2 x ArH, *J* = 7.1 Hz), 7.32 (t, 2H, 2 x ArH, *J* = 7.5 Hz), 7.27 – 7.23 (m, 1H, ArH), 5.95 (d,, 1H, CH, *J* = 1.3 Hz), 5.88 (ddt, 1H, CH, *J* = 16.6, 10.2, 6.3 Hz), 5.60 (s, 1H, CH), 5.23 (ddd, 1H, CH, *J* = 17.2, 3.2, 1.5 Hz), 5.19 – 5.15 (m, 1H, CH), 3.65 (s, 2H, CH_2), 3.29 (s, 2H, CH_2), 3.13 (d, 2H, CH_2, *J* = 6.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 135.4, 132.3, 128.9, 128.4, 127.1, 118.2, 117.9, 61.6, 57.5, 56.1.

Consistent with reported data.[243]

Compound 178, benzyl allylcarbamate



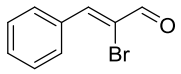
To a solution of allyl amine (757 µL, 10 mmol, 1 eq.) in MeCN was added Et_3N (2086 µL, 15 mmol, 1.5 eq.)and *N*-(benzyloxycarbonyloxy)succinimide (2.5 g, 10 mmol, 1 eq.) at room

temperature. The reaction was stirred at room temperature for 16 hours then diluted with water and washed between brine and DCM. The organic layers were dried with Na_2SO_4, concentrated in vacuo then purified by flash chromatography (20% EtOAc/PE) to afford the title compound as a yellow oil (1725 mg, 94%)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, 4H, 4 x ArH, *J* = 4.4 Hz), 7.34 – 7.29 (m, 1H, ArH), 5.90 – 5.80 (m, 1H, CH), 5.19 (dd, 1H, CH, *J* = 17.2, 1.3 Hz), 5.16 – 5.09 (m, 3H, 3 x CH), 4.82 (s, 1H, CH), 3.83 (s, 2H, CH_2).

Consistent with reported data.[244]

Compound 182, *(Z)*-2-bromo-3-phenylacrylaldehyde



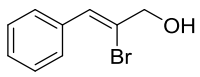
To an oven dried round bottom flask was dissolved *trans*-cinnamaldehyde (2514 µL, 20 mmol, 1 eq.) in dry DCM (40 mL). At 0 °C and under an atmosphere of nitrogen, Br_2 (1086 µL, 21.2 mmol, 1.06 eq.) was added dropwise. The reaction was stirred at room temperature for 15 minutes and then Et_3N (3066 µL, 22 mmol, 1.1 eq.) was added dropwise at 0 °C. After being stirred for 15 minutes at room temperature, the reaction was quenched with 1M HCl (aqueous). The mixture was washed between DCM and sodium metabisulfite (10 % in water), dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (4218 mg, >99%). ^{1}H NMR showed a 45:55 ratio of Z:E isomers, however, after 3 days of ageing at room temperature, full isomerisation to the *Z* isomer occurred (as a yellow solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1H, aldehyde CH), 8.01 (dd, 2H, 2 x ArH, *J* = 7.5, 1.8 Hz), 7.90 (s, 1H, alkene CH), 7.49 (d, 3H, 3 x ArH, *J* = 7.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ 187.3, 149.3, 132.9, 132.0, 129.3, 124.4 (1C not observed).

Consistent with reported data.[245]

Compound 183, *(Z)*-2-bromo-3-phenylprop-2-en-1-ol



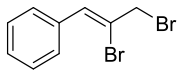
To a round bottom flask containing (*Z*)-2-bromo-3-phenylacrylaldehyde (2100 mg, 10 mmol, 1 eq.) in THF:H_2O (27 mL:3 mL) was added $NaBH_4$ (580 mg, 15 mmol, 1.5 eq.) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being quenched with NH_4Cl then washed between water and EtOAc, dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc) afforded the title compound as a clear oil (2109 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, 2H, 2 x ArH, *J* = 7.4 Hz), 7.40 – 7.34 (m, 2H, 2 x ArH), 7.34 – 7.29 (m, 1H, ArH), 7.09 (s, 1H, alkene CH), 4.42 (s, 2H, CH_2), 2.18 (br. s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.3, 129.4, 128.9, 128.5, 125.6, 69.9

Consistent with reported data.[246]

Compound 184, *(Z)*-2-bromo-3-phenylacrylaldehyde



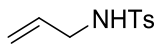
To an oven dried round bottom flask containing (*Z*)-2-bromo-3-phenylprop-2-en-1-ol (1060 mg, 5 mmol, 1 eq.) in dry DCM (25 mL) was added CBr_4 (2075 mg, 6.25 mmol, 1.25 eq.) and PPh_3 (1965 mg, 7.5 mmol, 1.5 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 16 h before being concentrated *in vacuo* and purified directly by flash chromatography (1% EtOAc) to afford the title compound as a clear oil (1360 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.60 (m, 2H, 2 x ArH), 7.42 – 7.31 (m, 3H, 3 x ArH), 7.14 (s, 1H, alkene CH), 4.44 (s, 2H, CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 134.8, 132.4, 129.2, 129.0, 128.4, 120.9, 40.8.

Consistent with reported data.[199]

Compound 185, *N*-allyl-4-methylbenzenesulfonamide



To an oven dried round bottom flask was dissolved tosyl chloride (1906 mg, 10 mmol, 1 eq.) in dry DCM (50 mL). At 0 °C, Et_3N (1530 µL, 11 mmol, 1.1 eq.) and allyl amine (825 µL, 11 mmol, 1.1 eq.) were added slowly. The reaction was stirred at room temperature for 16 hours

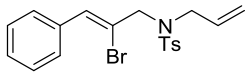
before being quenched with NH_4Cl. The mixture was washed between DCM and water, dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow solid (2089 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.73 (m, 2H, 2 x ArH), 7.34 – 7.28 (m, 2H, 2 x ArH), 5.78 – 5.66 (m, 1H, CH), 5.13 (dddd, 2H, CH_2, *J* = 23.8, 10.2, 2.7, 1.5 Hz), 4.65 – 4.48 (m, 1H, CH), 3.58 (tt, 2H, CH_2, *J* = 6.1, 1.5 Hz), 2.43 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.6, 137.1, 133.1, 129.9, 127.3, 117.8, 45.9, 21.6.

Consistent with reported data.[247]

Compound 186, (*Z*)-*N*-allyl-*N*-(2-bromo-3-phenylallyl)-4-methylbenzenesulfonamide



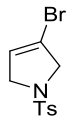
To an oven dried round bottom flask was added *N*-allyl-4-methylbenzenesulfonamide (384 mg, 1.82 mmol, 1 eq.) and dry DMF (7.5 mL). NaH (60% in mineral oil) (87 mg, 2.18 mmol, 1.2 eq.) was added at 0 °C and the white suspension was stirred at this temperature for 15 minutes. Following this, (*Z*)-(2,3-dibromoprop-1-en-1-yl)benzene (500 mg, 1.82 mmol, 1 eq.) in DMF (2.5 mL) was added dropwise and the white suspension became a dark orange solution. After stirring at room temperature for 45 minutes, the reaction was quenched with NH_4Cl and washed between EtOAc and 5% LiCl aqueous solution. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (7% EtOAc) afforded the title compound as a yellow oil (641 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.53 (d, 2H, 2 x ArH, *J* = 7.3 Hz), 7.38 – 7.28 (m, 5H, 5 x ArH), 6.93 (s, 1H, CH), 5.73 – 5.61 (m, 1H, CH), 5.21 (s, 1H, CH), 5.19 – 5.16 (m, 1H, CH), 4.24 (s, 2H, CH_2), 3.93 (d, 2H, CH_2, *J* = 6.5 Hz), 2.42 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 137.5, 135.0, 132.5, 130.7, 129.8, 129.1, 128.4, 128.3, 127.5, 120.7, 119.9, 55.9, 50.3, 29.8, 21.6.

Consistent with reported data.[199]

Compound 188, 3-bromo-1-tosyl-2,5-dihydro-1*H*-pyrrole



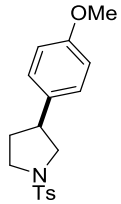
To an oven dried microwave vial was added Grubbs G2 catalyst (0.1 eq.) and the vial was sealed and purged. Dry benzene was added and the solution was stirred at 60 °C for 2 minutes before diene was added in a solution of benzene (1 mL). The reaction was stirred for 16 h at 60 °C then applied directly onto a column of silica. The title compound eluted at 8% EtOAc as an off-white amorphous solid (46 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.34 (d, 2H, 2 x ArH, *J* = 8.0 Hz), 5.81 – 5.78 (m, 1H, alkene CH), 4.19 – 4.12 (m, 2H, 2 x CH), 4.12 – 4.05 (m, 2H, 2 x CH), 2.44 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.1, 133.9, 130.1, 127.6, 125.8, 113.9, 58.7, 55.3, 21.7.

Consistent with reported data.[199]

Compound 189, 3-(4-methoxyphenyl)-1-tosylpyrrolidine



Synthesised according to General Procedure W using 3-bromo-1-tosyl-2,5-dihydro-1*H*-pyrrole (75 mg, 0.25 mmol, 1 equiv.) and 4-methoxyphenyl boronic acid (38 mg, 0.25 mmol, 1 eq.) and purified by flash column chromatography (7% EtOAc/PE) to afford the title compound an off-white amorphous solid (65.3mg, 79%).

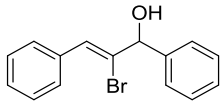
υ_{max} (neat): 2930, 2815, 1523, 1493 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.34 (d, 2H, 2 x ArH, *J* = 8.0 Hz), 7.01 (d, 2H, 2 x ArH, *J* = 8.6 Hz), 6.80 (d, 2H, 2 x ArH, *J* = 8.7 Hz), 3.77 (s, 3H, CH_3), 3.69 (dd, 1H, CH, *J* = 8.8, 6.8 Hz), 3.51 (ddd, 1H, CH, *J* = 10.0, 8.5, 3.1 Hz), 3.34 (td, 1H, CH, *J* = 9.5, 7.0 Hz), 3.22 – 3.11 (m, 2H, 2 x CH), 2.45 (s, 3H, CH_3), 2.20 – 2.12 (m, 1H, CH), 1.87 – 1.76 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 143.6, 134.2, 129.8, 128.0, 127.7, 114.2, 55.4, 54.4, 47.9, 43.3, 33.2, 21.7. (1C not observed).

HRMS ($C_{18}H_{22}NO_3S$) $[M+H]^+$ requires: 332.1315, observed: 332.1317

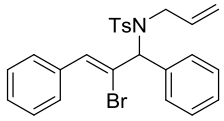
Compound 190, (*Z*)-2-bromo-1,3-diphenylprop-2-en-1-ol



To a solution of (*Z*)-2-bromo-3-phenylacrylaldehyde (105 mg, 0.5 mmol, 1 eq.) in THF (4 mL) was added PhMgBr (3M, 333 µL, 1 mmol, 2 eq.) at 0 °C. The reaction was stirred for 0.5 h before water was added and the mixture was washed between water and ethyl acetate. After drying with Na_2SO_4, the solution was concentrated *in vacuo* and used in the next step without purification. A ^{1}H NMR was taken of the crude material to ensure the formation of product.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, 2H, 2 x ArH, *J* = 7.4 Hz), 7.52 (d, 2H, 2 x ArH, *J* = 7.3 Hz), 7.46 – 7.33 (m, 6H, 6 x ArH), 7.31 (s, 1H, alkene CH), 5.49 (d, 1H, CH, *J* = 3.3 Hz) (1H not observed, exchangeable).

Compound 191, (*Z*)-*N*-allyl-*N*-(2-bromo-1,3-diphenylallyl)-4-methylbenzenesulfonamide



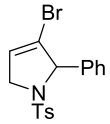
To an oven dried round bottom flask was containing (*Z*)-2-bromo-1,3-diphenylprop-2-en-1-ol (144 mg, 0.5 mmol, 1.2 eq.) in THF (5 mL) was added *N*-allyl-4-methylbenzenesulfonamide (88 mg, 0.41 mmol, 1 eq.) and triphenylphosphine (131 mg, 0.41 mmol, 1 eq.) at 0 °C. After stirring for 10 minutes at 0 °C, diisopropyl azodicarboxylate (101 mg, 0.41 mmol, 1 eq.) in THF (2.5 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 5 hours before being quenched with water and washed between water and ethyl acetate. The organic layer was dried with Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (7% EtOAc/PE) to afford the title compound as a clear, colourless oil (73 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.42 (dd, 2H, 2 x ArH, *J* = 7.7, 1.4 Hz), 7.37 – 7.22 (m, 10H, 10 x ArH), 6.81 (s, 1H, CH), 6.09 (s, 1H, CH), 5.56 – 5.41 (m, 1H, CH), 4.90 – 4.80 (m, 2H, 2 x CH), 4.00 – 3.83 (m, 2H, 2 x CH), 2.39 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 137.7, 136.5, 135.1, 134.8, 131.6, 129.7, 129.5, 129.2, 128.7, 128.5, 128.4, 128.2, 127.8, 123.7, 117.4, 69.6, 49.1, 21.6.

Consistent with reported data.[199]

Compound 192, 3-bromo-2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole



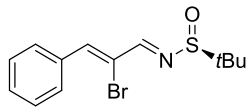
To an oven dried microwave vial was added Grubbs G2 catalyst (12 mg, 0.014 mmol, 0.1 eq.). The flask was capped and purged then benzene (1 mL) was added. After stirring for 2 minutes at 60 °C, (*Z*)-*N*-allyl-*N*-(2-bromo-1,3-diphenylallyl)-4-methylbenzenesulfonamide (67 mg, 0.14 mmol, 1 eq.) in benzene (1.8 mL) was added dropwise. The reaction was stirred for 16 h at 60 °C then purified directly by flash chromatography (10% EtOAc) to afford the title compound as a clear, colourless oil (37.7 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.34 – 7.30 (m, 3H, 3 x ArH), 7.27 – 7.23 (m, 2H, 2 x ArH), 7.19 (d, 2H, 2 x ArH, *J* = 8.0 Hz), 6.02 (dd, CH, *J* = 4.0, 2.0 Hz), 5.42 – 5.38 (m, 1H, CH), 4.36 (dt, 1H, CH, *J* = 14.2, 2.5 Hz), 4.24 (ddd, 1H, CH, *J* = 14.2, 5.8, 2.0 Hz), 2.41 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 138.2, 135.4, 129.7, 128.6, 128.2, 127.4, 125.5, 119.8, 73.0, 55.1, 21.6.

Consistent with reported data.[199]

Compound 194, (*S*)-*N*-((1E,2Z)-2-bromo-3-phenylallylidene)-2-methylpropane-2-sulfinamide



To a solution of (*Z*)-2-bromo-3-phenylacrylaldehyde (422 mg, 2 mmol, 1 eq.) in DCM (8 mL) was added (*R*)-2-methyl-2-propanesulfinamide (242 mg, 2 mmol, 1 eq.) and Cs_2CO_3 (704 mg, 2 mmol, 1 eq.) and the reaction was stirred at 40 °C with a reflux condenser for 16 h. Following this, the reaction was filtered through Celite, rinsed with DCM and concentrated *in vacuo*. Purification by flash chromatography (14% EtOAc) gave the title compound as a yellow oil (521.2 mg, 83%).

υ_{max} (neat): 3100, 2977, 1726, 1709, 1519 cm^{-1}

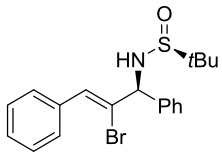
^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H, imine CH), 7.95 – 7.88 (m, 2H, 2 x ArH), 7.64 (s, 1H, alkene CH), 7.48 – 7.40 (m, 3H, 3 x ArH), 1.27 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 144.7, 134.0, 130.7, 130.6, 128.7, 120.9, 58.4, 22.7.

HRMS ($C_{13}H_{17}NOS$) $[M+H]^+$ requires: 316.0187, observed: 316.0187

$[\alpha]_D^{20}$: +18.6 (c=0.1, CH_2Cl_2)

Compound 195, (S)-N-((S,Z)-2-bromo-1,3-diphenylallyl)-2-methylpropane-2-sulfinamide



To a solution of (*S*)-*N*-((1E,2Z)-2-bromo-3-phenylallylidene)-2-methylpropane-2-sulfinamide (500 mg, 1.59 mmol, 1 eq.) in dry toluene (10 mL) was added PhMgBr (3M in Et_2O) (793 µL, 2.38 mmol, 1.5 eq.) dropwise at -40°C. The reaction was stirred for 5 h at -40 °C before being quenched with NH_4Cl and washed between water and ethyl acetate. The organic layer was dried with Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (55% EtOAc/PE) to afford the title compound as a clear oil (330.3 mg, 53%).

υ_{max} (neat): 3107, 2988, 1729, 1709, 1517 cm^{-1}

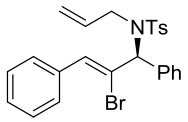
^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 2H, 2 x ArH, *J* = 7.3 Hz), 7.50 (d, 2H, 2 x ArH, *J* = 7.3 Hz), 7.42 – 7.29 (m, 7H, 6 x ArH, 1 x alkene CH), 5.38 (d, 1H, CH, *J* = 3.4 Hz), 3.76 (d, 1H, CH, *J* = 3.2 Hz), 1.32 (s, 9H, 3 xCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.4, 135.1, 130.9, 129.4, 128.9, 128.6, 128.5, 128.3, 127.6, 127.1, 66.4, 56.3, 22.9.

HRMS ($C_{19}H_{23}NOS$) $[M+H]^+$ requires: 394.0657, observed: 394.0655

$[\alpha]_D^{20}$: +8.9 (c=0.1, CH_2Cl_2)

Compound 200, (*S*,*Z*)-*N*-allyl-*N*-(2-bromo-1,3-diphenylallyl)-4-methylbenzenesulfonamide



To a solution of (S)-*N*-((S,Z)-2-bromo-1,3-diphenylallyl)-2-methylpropane-2-sulfinamide (300 mg, 0.77 mmol, 1 eq.) in MeOH (2 mL) was added AcCl (540 µL, 7.7 mmol, 10 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 1 h before being concentrated *in vacuo*. The resulting HCl salt was taken up in MeCN (4 mL) and K_2CO_3 (638, 4.62 mmol, 6 eq.) was added. After stirring for 15 minutes at room temperature, allyl bromide (80 µL, 0.92, 1.2 eq.) was added dropwise. The reaction was stirred 60 °C for 6 h before being quenched with NH_4Cl. The mixture was washed between water and EtOAc and the organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. To this was added pyridine (3 mL) and tosyl chloride (195 µL, 1.54 mmol, 2 eq.)and the reaction was stirred at room temperature for 16 h. HCl (1M) was added and the mixture was washed with DCM. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography (10% EtOAc/PE) to afford the title compound as a yellow oil (122.2 mg, 33%, >99% ee).

υ_{max} (neat): 3057, 2920, 1597, 1493, 1342 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.45 – 7.39 (m, 2H, 2 x ArH), 7.37 – 7.24 (m, 10H, 10 x ArH), 6.80 (s, 1H, alkene CH), 6.09 (s, 1H, CH), 5.53 – 5.41 (m, 1H, CH), 4.90 – 4.79 (m, 2H, 2 x CH), 4.03 – 3.81 (m, 2H, CH_2), 2.40 (s, 3H, CH_3)

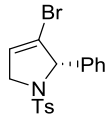
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.7, 136.5, 135.1, 134.8, 131.6, 129.7, 129.4, 129.4, 129.2, 128.7, 128.5, 128.4, 128.2, 127.8, 123.7, 117.4, 69.56, 49.1, 21.6.

HRMS ($C_{25}H_{28}N_2O_2S$) $[M+NH_4]^+$ requires: 501.1029, observed: 501.1022

$[\alpha]_D^{20}$: -2.4 (c=0.05, CH_2Cl_2)

%ee: >99% (by chiral HPLC)

Compound 201, (*S*)-3-bromo-2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole



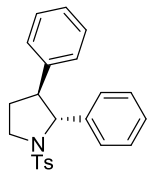
To an oven dried 2-5 mL microwave vial was added Grubbs G2 catalyst (17 mg, 0.02 mmol, 0.1 eq.). The vial was capped, dry benzene (2 mL) was added and the reaction was stirred for 5 minutes at 60 °C. Following this, (*S*,Z)-*N*-allyl-*N*-(2-bromo-1,3-diphenylallyl)-4-methylbenzenesulfonamide (100 mg, 0.2 mmol, 1 eq.) in dry benzene (2 mL) was added dropwise at 60 °C. The reaction was stirred at 60 °C for 16 h then was purified directly by flash chromatography (7% EtOAc/PE) to afford the title compound as an orange oil (56.6 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, 2 x ArH, *J* = 8.3 Hz), 7.32 – 7.27 (m, 3H, 3 x ArH), 7.25 – 7.20 (m, 2H, 2 x ArH), 7.17 (d, 2H, 2 x ArH, *J* = 8.0 Hz), 5.99 (dd, 1H, CH, *J* = 4.0, 2.0 Hz), 5.40 – 5.36 (m, 1H, CH), 4.33 (dt, 1H, CH, *J* = 14.2, 2.5 Hz), 4.21 (ddd, 1H, CH, *J* = 14.2, 5.8, 2.0 Hz), 2.38 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.6, 138.2, 135.4, 129.7, 128.6, 128.2, 127.4, 125.5, 119.8,73.0, 55.1, 21.6.

HRMS ($C_{11}H_{11}NO_4Br$) $[M+H]^+$ requires: 299.9872, observed: 299.9868

Compound 202, (2*R*,3*S*)-2,3-diphenyl-1-tosylpyrrolidine (12:1, *trans:cis*)



Synthesised according to General Procedure B using phenyl boronic acid (31 mg, 0.25 mmol, 1 equiv.) and (*S*)-3-bromo-2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (95 mg, 0.25 mmol, 1

equiv.), and purified by flash column chromatography (14% EtOAc/PE) to afford the title compound an off-white amorphous solid (66.0 mg, 70%).

υ_{max} (neat): 3002, 2990, 2713, 1515, cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.29 (d, 2H, 2 x ArH, *J* = 8.2 Hz), 7.10 – 6.99 (m, 6H, 6 x ArH), 6.74 (d, 2H, 2 x ArH, *J* = 7.2 Hz), 6.65 (d, 2H, 2 x ArH, *J* = 6.6 Hz), 5.03 (d, 1H, CH, *J* = 8.1 Hz), 3.87 (t, 1H, CH, *J* = 8.7 Hz), 3.52 (ddd, 1H, CH, *J* = 10.9, 9.6, 6.6 Hz), 3.29 (ddd, 1H, CH, *J* = 13.6, 8.0, 5.7 Hz), 2.44 (s, 3H, CH_3), 2.41 – 2.34 (m, 1H, CH), 2.06 (dt, 1H, CH, *J* = 12.3, 6.1 Hz).

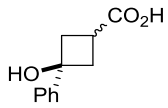
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5, 138.8, 137.0, 135.5, 129.7, 128.6, 128.0, 127.6, 127.6, 127.5, 127.0, 67.2, 50.6, 48.0, 27.8, 21.7.

cis isomer observed in ^{1}H and ^{13}C NMR but not reported. Diastereomeric ratio determined by ^{1}H NMR, ratio between doublet at 5.03 and 4.65.

HRMS ($C_{23}H_{24}O_2NS$) $[M+H]^+$ requires: 378.1522, observed: 378.1522

ee = >97% (by chiral HPLC)

Compound 203, 3-hydroxy-3-phenylcyclobutane-1-carboxylic acid



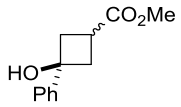
To a solution of 3-oxocyclobutanecarboxylic acid (114 mg, 1 mmol, 1 eq.) in THF (3 mL) was added phenyl magnesium bromide (1M, 1.1 mL, 1.1 mmol, 1.1 eq.) at 0°C. The reaction was stirred at 0 °C for 6 h before being quenched with NH_4Cl. The mixture was washed between ethyl acetate and water, then ethyl acetate and brine before being dried with Na_2SO_4. Concentration *in vacuo* afforded the title compound as a clear oil (191 mg, 99%) as a mixture of diastereomers (trans isomer major according to previous reports).[248]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 2H, 2 x ArH, *J* = 7.4 Hz), 7.40 (t, 2H, 2 x ArH, *J* = 7.7 Hz), 7.32 (t, 1H, ArH, *J* = 7.3 Hz), 2.96 – 2.88 (m, 2H, 2 x CH), 2.72 – 2.67 (m, 2H, 2 x CH) (2H not observed, exchangeable).

^{13}C NMR (101 MHz, DMSO-d_6): δ 177.0, 145.4, 128.1, 126.7, 124.9, 71.0, 41.1 (1C not observed).

Consistent with reported data.[248]

Compound 204, methyl 3-hydroxy-3-phenylcyclobutane-1-carboxylate



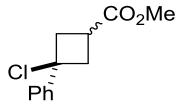
To a flask containing 3-hydroxy-3-phenylcyclobutane-1-carboxylic acid (192 mg, 1 mmol, 1 eq.) was added HCl/MeOH (5 mL). The reaction was stirred for 3 hours before being concentrated *in vacuo* to afford the title compound as a clear gum (192 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 – 7.52 (m, 2H, 2 x ArH), 7.39 – 7.25 (m, 3H, 3 x ArH), 3.75 (s, 3H, CH_3), 2.90 – 2.80 (m, 3H, 3 x CH), 2.70 – 2.59 (m, 2H, 2 x CH) (1H missing, exchangeable).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.6, 144.8, 128.3, 127.7, 125.0, 13.2, 52.1, 41.0, 29.3

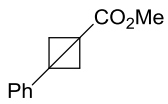
Consistent with reported data.[248]

Compound 205, methyl 3-chloro-3-phenylcyclobutane-1-carboxylate



To a solution of methyl 3-hydroxy-3-phenylcyclobutane-1-carboxylate (206 mg, 1 mmol, 1 eq.) in toluene (5 mL) was added conc. HCl (1 mL, 12 mmol, 12 eq.) and the reaction mixture was sonicated for 6 h at room temperature. Following this, the mixture was separated between water and ethyl acetate, then brine and ethyl acetate. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide the title compound which was used in the next step without further purification.

Compound 206, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate

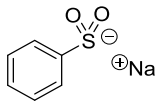


To a solution of crude methyl 3-chloro-3-phenylcyclobutane-1-carboxylate (224 mg, 1 mmol, 1 eq.) in THF (5 mL) was added NaH (60 mg, 1.5 mmol. 1.5 eq.) at 0 °C. The reaction was stirred at room temperature for 3 h before being quenched with NH_4Cl and washed between water and ethyl acetate. After being dried with Na_2SO_4, the organic layer was concentrated *in vacuo* and purified by flash chromatography (10% EtOAc/PE) to afford the title compound as a white solid (169 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 5H, 5 x ArH), 3.77 – 3.72 (m, 2H, 2 x CH), 3.49 (s, 3H, CH_3), 2.93 (s, 2H, 2 x CH).

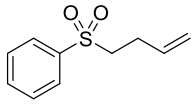
Consistent with reported data.[249]

Compound 208, sodium benzenesulfinate



To a flask containing benzenesulfonyl chloride (6 mL, 47 mmol, 1 eq.) was added H_2O (100 mL), Na_2SO_3 (12 g, 95.2 mmol, 2 eq.) and the reaction was heated to 80 °C. $NaHCO_3$ (8 g, 95.2 mmol, 2 eq.) was added portionwise over *ca*. 30 minutes and a reflux condenser was fitted. The reaction was stirred at 80 °C for 16 h. The reaction mixture was allowed to cool to room temperatuyre and the water was removed in vacuo. Toluene (*ca*. 100 mL) was used to azeotrope the remaining water and then hot MeOH (50 mL) was added and the suspension was filtered to leave behind a yellow solid. This was repeated with several times to ensure full transfer of product. The combined filtrate was concentrated *in vacuo* to give an off-white solid which was used directly in the next step without further purification.

Compound 209, (but-3-en-1-ylsulfonyl)benzene



Sodium benzenesulfinate (7.7 g, 47 mmol, 1 eq.) was dissolved in DMF (100 mL) at room temperature and 4- bromobut-1-ene (5.72 mL, 56.4 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at 60 °C for 2 h. Following this, the reaction was quenched with H_2O and washed between water and EtOAc, then LiCl (5% aqueous solution) and EtOAc. The organic layer was dried with Na2SO4 and concentrated *in vacuo*. The crude material was purified by

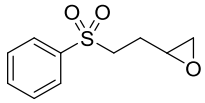
flash chromatography (20% EtOAc/PE) to afford the title compound as a clear oil (7.45 g, 81%)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 – 7.88 (m, 2H, 2 x ArH), 7.68 – 7.63 (m, 1H, ArH), 7.57 (t, 2H, 2 x ArH, *J* = 7.7 Hz), 5.72 (ddt, 1H, alkene CH, *J* = 16.8, 10.2, 6.5 Hz), 5.07 – 5.00 (m, 2H, 2 x alkene CH), 3.18 – 3.14 (m, 2H, CH_2), 2.49 – 2.42 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 133.9, 129.4, 128.2, 117.3, 55.5, 26.9.

Consistent with reported data.[208]

Compound 210, 2-(2-(phenylsulfonyl)ethyl)oxirane



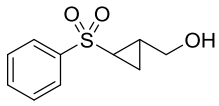
To a solution of (but-3-en-1-ylsulfonyl)benzene (8.82 g, 45 mmol, 1 eq.) in acetone (100 mL) and H_20 (100 mL) was added oxone (9.3 g, 61.1 mmol, 1.3 eq) and $NaHCO_3$ (19.7 g, 235 mmol, 5 eq). The solution was stirred at room temperature for 16 h, at which point oxone and $NaHCO_3$ (as above) were added, along with acetone (100 mL) and H_2O (100 mL). After stirring for a further 3 h, the reaction was quenched with $Na_2S_2O_5$ in water. The solution was filtered through Celite and the filtrate was washed between EtOAc and water. The organic layer was dried using Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (30% EtOAc/PE) to afford the title compound as a clear oil (6.01 g, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 – 7.89 (m, 2H, 2 x ArH), 7.66 (t, 1H, ArH, *J* = 7.5 Hz), 7.57 (t, 2H, 2 x ArH, *J* = 7.7 Hz), 3.24 – 3.19 (m, 2H, CH_2), 3.02 – 2.96 (m, 1H, CH), 2.78 – 2.74 (m, 1H, CH), 2.48 (dd, 1H, CH, *J* = 4.8, 2.6 Hz), 2.19 – 2.11 (m, 1H, CH), 1.89 – 1.75 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0, 134.0, 129.5, 128.2, 52.8, 50.2, 47.2, 26.0.

Consistent with reported data.[208]

Compound 211, (2-(phenylsulfonyl)cyclopropyl)methanol



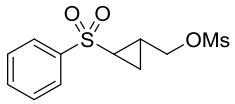
To a solution of 2-(2-(phenylsulfonyl)ethyl)oxirane (4.24 g, 20 mmol, 1 eq.) in THF (130 mL) was added *n*-BuLi (1.9 M in THF; 10.5 mL, 20 mmol, 1 eq.) dropwise at 0 °C. The reaction mixture was left to stir for 5 minutes at 0°C before being quenched with NH4Cl and washed between water and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (4239 mg, 100%) without the need for further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 – 7.86 (m, 2H, 2 x ArH), 7.62 (t, 1H, ArH, *J* = 7.4 Hz), 7.56 – 7.51 (m, 2H, 2 x ArH), 3.66 (dd, 1H, CH, *J* = 11.6, 5.1 Hz), 3.47 (dd, 1H, CH, *J* = 11.6, 6.0 Hz), 2.49 – 2.44 (m, 1H, CH), 2.05 – 1.98 (m, 1H, CH), 1.43 (dt, 1H, CH, *J* = 10.0, 5.2 Hz), 1.09 – 1.03 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5, 133.6, 129.4, 127.6, 61.9, 36.9, 21.6, 10.2.

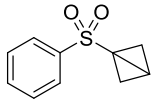
Consistent with reported data.[208]

Compound 212, (2-(phenylsulfonyl)cyclopropyl)methyl methanesulfonate



To a solution of (2-(phenylsulfonyl)cyclopropyl)methanol (2.12 g, 10 mmol, 1 eq.) in DCM (65 mL) was added Et_3N (1.67 mL, 12 mmol, 1.2 eq.) at 0 °C. Next, methanesulfonyl chloride (0.93 mL, 12 mmol, 1.2 eq.) was added dropwise at °C and the reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with DCM and was washed with 1M HCl (aq.) and water, and then the organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound which was used directly in the next step.

Compound 213, 1-(phenylsulfonyl)bicyclo[1.1.0]butane



To a solution of crude (2-(phenylsulfonyl)cyclopropyl)methyl methanesulfonate (assumed 2.9 g, 10 mmol, 1 eq.) in THF (200 mL) was added *n*-BuLi (2M, 5 mL, 10 mmol, 1 eq.) dropwise

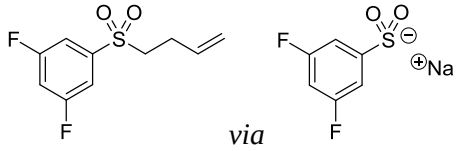
at 0 °C and the reaction was stirred at 0 °C for 5 minutes. Next, NH_4Cl was added and the mixture was washed between water and DCM. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/PE) afforded the title compound as a white solid (422 mg, 22%). Increasing the eluent to 50% EtOAc/PE recovered the starting material ((2-(phenylsulfonyl)cyclopropyl)methyl methanesulfonate).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, 2H, 2 x ArH, *J* = 7.5 Hz), 7.62 (t, 1H, ArH, *J* = 7.3 Hz), 7.56 (t, 2H, 2 x ArH, *J* = 7.6 Hz), 2.59 – 2.54 (m, 1H, CH), 2.52 (d, 2H, CH_2, *J* = 3.5 Hz), 1.39 (d, 2H, CH_2, *J* = 2.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.1, 133.2, 129.3, 127.2, 38.4, 23.2, 12.7.

Consistent with reported data.[208]

Compound 215, 1-(but-3-en-1-ylsulfonyl)-3,5-difluorobenzene



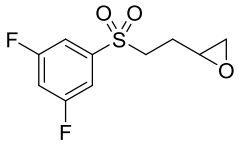
To a flask containing 3,5-difluorobenzenesulfonyl chloride (10 g, 47 mmol, 1 equiv.) was added H_2O (100 mL), Na_2SO_3 (12 g, 95.2 mmol, 2 eq.) and the reaction was heated to 80 °C. $NaHCO_3$ (8 g, 95.2 mmol, 2 eq.) was added portionwise over *ca*. 30 minutes and a reflux condenser was fitted. The reaction was stirred at 80 °C for 16 h. The reaction mixture was allowed to cool to room temperatuyre and the water was removed in vacuo. Toluene (*ca*. 100 mL) was used to azeotrope the remaining water and then hot MeOH (50 mL) was added and the suspension was filtered to leave behind a yellow solid. This was repeated with several times to ensure full transfer of product. The combined filtrate was concentrated *in vacuo* to give an off-white solid which was used directly in the next step without further purification. The crude sodium 3,5-difluorobenzenesulfinate was dissolved in DMF (100 mL) at room temperature and 4-bromobut-1-ene (5.72 mL, 56.4 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at 60 °C for 2 h. Following this, the reaction was quenched with H_2O and washed between water and EtOAc, then LiCl (5% aqueous solution) and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (20% EtOAc/PE) to afford the title compound as a clear oil which was used directly in the next step without further purification (4.04 g, 37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.43 (m, 2H, 2 x ArH), 7.12 (tt, 1H, ArH, *J* = 8.4, 2.3 Hz), 5.73 (ddt, 1H, alkene CH, *J* = 16.9, 10.3, 6.5 Hz), 5.12 – 5.06 (m, 2H, 2 x alkene CH), 3.22 – 3.15 (m, 2H, CH_2), 2.53 – 2.45 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.11 (dd, $^{1}J_{CF}$ = 255.9, $^{3}J_{CF}$ = 11.5 Hz), 142.48 (t, $^{3}J_{CF}$ = 7.7 Hz), 133.34, 117.78, 112.0 (dd, $^{2}J_{CF}$ = 21, $^{4}J_{CF}$ = 7.2 Hz), 109.68 (t, $^{2}J_{CF}$ = 25.1 Hz), 55.37, 26.83.

Consistent with reported data.[208]

Compound 216, 2-(2-((3,5-difluorophenyl)sulfonyl)ethyl)oxirane



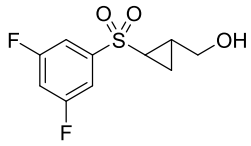
To a solution of 1-(but-3-en-1-ylsulfonyl)-3,5-difluorobenzene (2320 mg, 10 mmol, 1 eq.) in acetone (50 mL) and H_20 (50 mL) was added oxone (4.6 g, 30.5 mmol, 3 eq) and $NaHCO_3$ (19.7 g, 110 mmol, 10 eq). The solution was stirred at room temperature for 16 h, at which point oxone and $NaHCO_3$ (as above) wad added, along with acetone (100 mL) and H_2O (100 mL). After stirring for a further 3 h, the reaction was quenched with $Na_2S_2O_5$ in water. The solution was filtered through Celite and the filtrate was washed between EtOAc and water. The organic layer was dried using Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (30% EtOAc/PE) to afford the title compound as a clear oil (2.3 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H, 2 x ArH), 7.13 (tt, 1H, ArH, *J* = 8.4, 2.3 Hz), 3.25 (t, 2H, 2 x CH, *J* = 7.9 Hz), 3.02 (td, 1H, CH, *J* = 6.7, 3.9 Hz), 2.80 (t, 1H, CH, *J* = 5.0 Hz), 2.52 (dd, 1H, CH, *J* = 4.7, 2.6 Hz), 2.26 – 2.17 (m, 1H, CH), 1.87 – 1.77 (m, 1H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.14 (dd, $^{1}J_{CF}$ = 256.2, $^{3}J_{CF}$ = 11.4 Hz), 142.35 (t, $^{3}J_{CF}$, *J* = 8.0 Hz), 111.88 (dd, $^{2}J_{CF}$ = 20.9, $^{4}J_{CF}$ = 7.6 Hz), 109.81 (t, $^{2}J_{CF}$, *J* = 25.0 Hz), 52.76, 49.99, 47.22, 25.85.

Consistent with reported data.[208]

Compound 217, (2-((3,5-difluorophenyl)sulfonyl)cyclopropyl)methanol



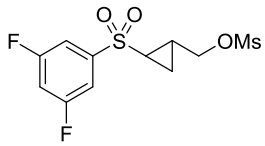
To a solution of 2-(2-((3,5-difluorophenyl)sulfonyl)ethyl)oxirane (4.24 g, 20 mmol, 1 eq.) in THF (130 mL) was added *n*-BuLi (1.9 M in THF; 10.5 mL, 20 mmol, 1 eq.) dropwise at 0°C. The reaction mixture was left to stir for 5 minutes at 0°C before being quenched with NH4Cl and washed between water and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (4239 mg, 100%) without the need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 2H, 2 x ArH), 7.15 – 7.01 (m, 1H, ArH), 3.76 (dd, 1H, CH, *J* = 11.5, 4.8 Hz), 3.49 (dd, 1H, CH, *J* = 11.5, 6.0 Hz), 2.50 (dt, 1H, CH, *J* = 8.3, 4.7 Hz), 2.19 (br. s, 1H, OH), 2.09 – 2.00 (m, 1H, CH), 1.49 – 1.42 (m, 1H, CH), 1.14 (ddd, 1H, CH, *J* = 8.2, 6.5, 5.6 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (dd, $^1J_{CF}$ = 255.4, $^3J_{CF}$ = 11.4 Hz), 143.7 (t, $^3J_{CF}$ = 8.2 Hz), 111.3 (dd, $^2J_{CF}$ = 28.3, $^4J_{CF}$ = 8.1 Hz), 109.3 (t, $^2J_{CF}$ = 25.2 Hz), 61.6, 36.5, 21.9, 10.3.

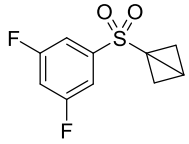
Consistent with reported data.[208]

Compound 218, (2-((3,5-difluorophenyl)sulfonyl)cyclopropyl)methyl methanesulfonate



To a solution of (2-((3,5-difluorophenyl)sulfonyl)cyclopropyl)methanol (2.48 g, 10 mmol, 1 eq.) in DCM (65 mL) was added Et_3N (1.67 mL, 12 mmol, 1.2 eq.) at 0 °C. Next, methanesulfonyl chloride (0.93 mL, 12 mmol, 1.2 eq.) was added dropwise at °C and the reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with DCM and was washed with 1M HCl (aq.) and water, and then the organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound which was used directly in the next step.

Compound 219, 1-(phenylsulfonyl)bicyclo[1.1.0]butane



To a solution of crude (2-(phenylsulfonyl)cyclopropyl)methyl methanesulfonate (assumed 3.26 g, 10 mmol, 1 eq.) in THF (200 mL) was added *n*-BuLi (2M, 5 mL, 10 mmol, 1 eq.) dropwise at 0 °C and the reaction was stirred at 0 °C for 5 minutes. Next, NH_4Cl was added and the mixture was washed between water and DCM. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/PE) afforded the title compound as a white solid (368 mg, 16%). Increasing the eluent to 50% EtOAc/PE recovered the starting material (2-((3,5-difluorophenyl)sulfonyl)cyclopropyl)methyl methanesulfonate

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 – 7.44 (m, 2H, 2 x ArH), 7.10 (tt, 1H, ArH, J = 8.3, 2.4 Hz), 2.71 – 2.68 (m, 1H, CH), 2.56 (dt, 2H, 2 x CH, J = 3.7, 1.3 Hz), 1.47 – 1.44 (m, 2H, 2 x CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (dd, $^1J_{CF}$ = 245, $^3J_{CF}$ = 11.2 Hz), 146.0 (t, $^3J_{CF}$ = 8.0 Hz), 111.0 (dd, $^2J_{CF}$ = 27.9, $^4J_{CF}$ = 7.5 Hz), 108.9 (t, $^2J_{CF}$ = 24.8 Hz), 38.8, 22.75, 14.0 (1C missing, coincidental).

Consistent with reported data.[208]

7. References

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